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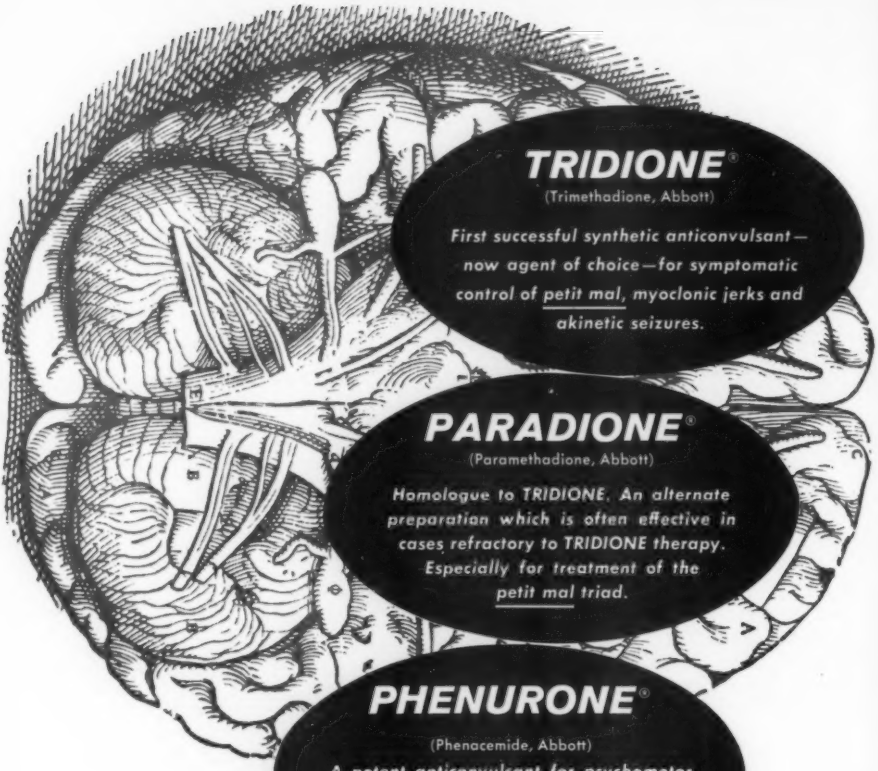

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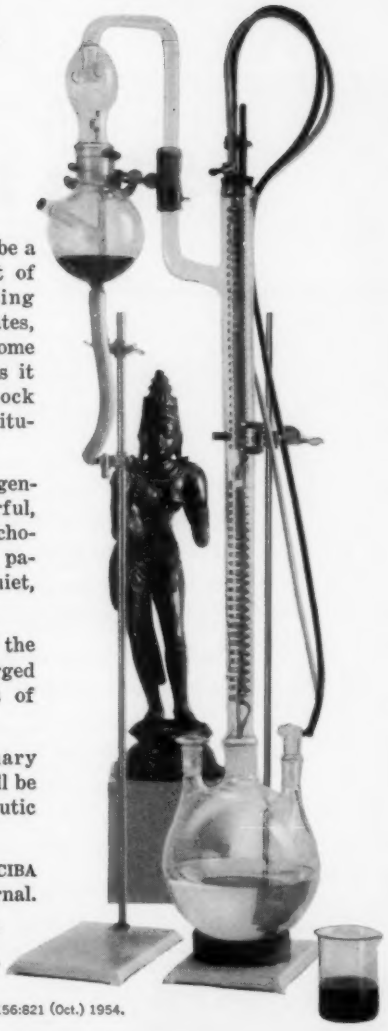

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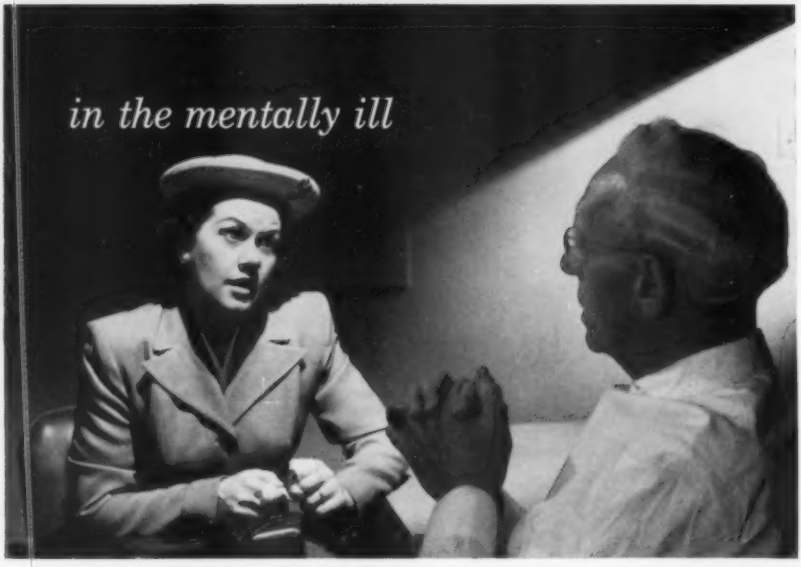

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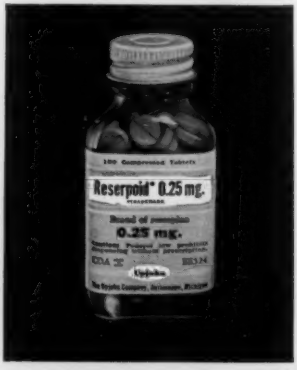

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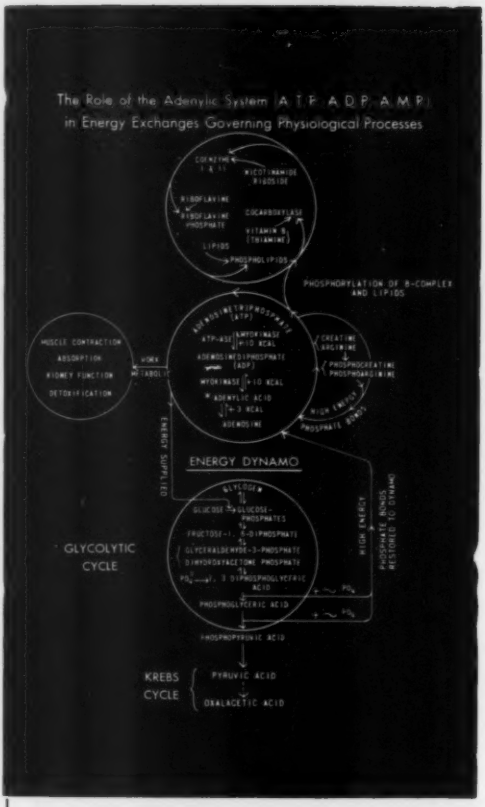

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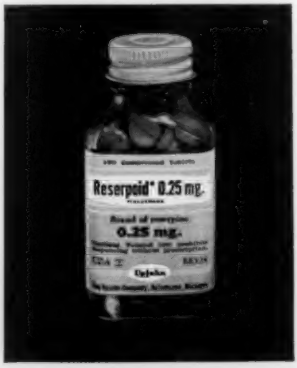

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Volume 5 Neurology *Number 5*

Pseudohypoparathyroidism

Clinical Picture and Relation to Convulsive Seizures

Boy Frame, M.D. and Sidney Carter, M.D.

PSEUDOHYPOPARATHYROIDISM is a clinical entity not frequently considered in the differentiation of the various conditions with which convulsions are associated. Many patients reported as having pseudohypoparathyroidism have been followed in clinics for convulsive disorders for a number of years before the correct diagnosis was established.

Albright and his associates[1] were the first to draw attention to the syndrome in 1942, and subsequently about 24 cases have been reported in the world literature.[2–17] The clinical picture is similar to that of idiopathic hypoparathyroidism, but in addition patients with pseudohypoparathyroidism tend to have a short, broad stature, a round facies, and an abnormal shortening of several or all of the fingers and toes. Ectopic ossifications of the soft tissues are also noted frequently.

The purpose of this paper is to present another case of pseudohypoparathyroidism in the hope that it may contribute to general awareness of the clinical picture. In most cases an early diagnosis followed by proper therapy will result in symptomatic improvement. The more pertinent features of the previously reported cases will also be discussed.

Two cases reported as pseudohypoparathyroidism are not included in the present study. The case of Lowe and associates[18] had an accompanying steatorrhea which complicated evaluation of the calcium metabolism. It is thought that the case of Berardinelli[19] did not offer sufficient data to establish the diagnosis of pseudohypoparathyroidism. On the other hand, one of the cases reported by Lachman[20] as having idiopathic hypoparathyroidism may have been a case of pseudohypoparathyroidism.

From the department of neurology, College of Physicians and Surgeons, Columbia University, and the Neurological Institute of the Presbyterian Hospital, New York City.

However, since data with regard to response to parathormone is lacking, it is not included in the present series.

CASE HISTORY

A nine year old white girl was admitted to the Neurological Institute of New York for the third time on July 22, 1954 because of uncontrolled seizures. She was born at term without complications, but her development was slow. She started to walk at 20 months and first began to say single words at 30 months. Her height was consistently less than other children her age. Since early infancy, it had been noted that she had a full, round facies and that her hands were short and stubby. School work had always been difficult and she was still in the second grade at age nine.

At the age of seven and a half years she had her first seizure, characterized by loss of consciousness and generalized clonic movements and followed by deep sleep. At age eight she had a similar generalized attack, following which there was moderate weakness of the right arm and leg lasting several days. In May 1953 she was admitted to the Neurological Institute of New York for the first time. Slight obesity was noted. On neurologic examination she was thought to have a mild, right hemiparesis, which cleared after several days. The left plantar response was extensor, the right equivocal. Blood chemistries disclosed a nonprotein nitrogen of 30 mg. per cent and a fasting blood sugar of 79 mg. per cent. An electroencephalogram revealed a disorganized record with a good deal of poorly formed, mostly low to medium voltage 3-5/second activity. In response to hyperventilation, synchronous bursts of high voltage regular 3/second wave and spike activity occurred within 20 seconds in both parietal and occipital areas. This record was interpreted as compatible with a convulsive disorder. Chest and skull roentgenograms were considered within normal limits. The patient was then discharged and followed in the clinic on phenobarbital 0.03 gm. twice a day.

In August 1953 seizures recurred and became more frequent. They began with a stiffening of the right arm and leg which lasted several hours without clonic movements. In the majority of these episodes there was no loss of consciousness. Dilantin was added to her medication, but ataxia and a rash necessitated its withdrawal. Mysoline 0.25 gm. twice a day was then prescribed. On this medication she was seizure free for a four month period, but had episodic clumsiness of the right arm. At times she complained of double vision.

In January 1954 she was admitted the second time for further study. Neurologic examination was similar to that described on her first admission, except the right hemiparesis was not present. The electroencephalogram again showed a moderately disorganized record consistent with a convulsive disorder. A pneumoencephalogram showed slight asymmetry of the ventricular system with minimal bulging of the anterior and middle portions of the body of the left lateral ventricle, the cause of which was not apparent. Bilateral carotid arteriography was then carried out and was thought to be within normal limits. The patient was discharged as a brain tumor suspect and followed in the clinic.

She was maintained on Mysoline 0.25 gm. twice a day and for three months was free of seizures. Following this, however, the attacks became more frequent, occurring almost daily. These were all similar in nature and began with numbness of the right arm and leg followed by a stiffening of the right arm, with no clonic movements and only occasional loss of consciousness. Sometimes the left arm and leg would become similarly involved. At this time she complained of tingling sensations in her hands. Her speech became thick and slurred. During a clinic visit it was noted that a strongly positive Chvostek sign was present. Her serum calcium was found to be 6.7 mg. per cent, and she was admitted to the hospital the third time for further evaluation.

The family history was of interest in that the patient's mother, age 37, was five feet tall and had a full, round facies similar to the patient. Her hands appeared somewhat short and broad, but x-rays did not show any abnormal shortening of the metacarpals. However, there was moderate soft tissue ossification about the left shoulder and to a lesser extent over the dorsum of the left foot. Serum calcium was 9.4 mg. per cent. A maternal uncle, age 41, had been operated on three times for a nontraumatic calcific bursitis of the left hip. X-rays of the left femur showed several small exostoses on the greater trochanter, as well as extensive calcium deposition in the soft tissues about the

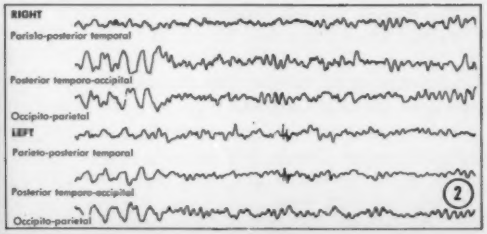

FIG. 1. Patient showing broad, round facies and short, stubby fingers.
FIG. 2. Electroencephalogram showing features of a general convulsive disorder. (See text).
FIG. 3. Roentgenograms of hands showing short metacarpals, especially fourth and fifth on the right. Bony demineralization is also noted.

left hip. There was no evidence of shortened metacarpals on x-rays and serum calcium was 9.2 mg. per cent. The patient's three and 12 year old sisters were well and had no resemblance to the patient. Their serum calcium determinations were normal.

Examination at the time of her third admission revealed the patient to be a dull appearing child of short stature, with a broad full facies and eyes set rather widely apart (figure 1). Her height was 49.5 inches and her weight 65 pounds. Dentition was poor with delayed eruption. There were no cataracts, and the texture of the hair and skin was normal. The hands were short and broad; in particular, the fourth and fifth fingers of both hands were abnormally short. The third, fourth, and fifth toes of both feet were also disproportionately short. Circumference of the head was 19.3 inches. Blood pressure was 90/60. The thyroid was not palpable. Examination of the heart, lungs, and abdomen was not remarkable.

On neurologic examination gait was observed to be moderately unsteady. No muscular weakness was demonstrated. Succession movements were slightly impaired in the upper extremities. Speech was slow and moderately slurred. Some of these signs were thought possibly to be due to Mysoline toxicity. The deep tendon reflexes were depressed throughout and both plantar responses were intermittently extensor. A 4+ bilateral Chvostek sign was present and the major peripheral nerves were hyperactive to direct percussion. The Trousseau sign was absent. Sensation was normal to all modalities. Fundoscopic examination revealed a slight blurring of the entire disk margin in the left eye only. The remainder of the cranial nerve examination was essentially normal.

Laboratory data

Hemoglobin was 13.8 gm.; white blood cell count, 7200 with normal differential; erythrocyte sedimentation rate, 8 mm./1 hr.

Urine showed specific gravity of 1.022; acid reaction, negative for albumin and glucose; and a negative Sulkowitch reaction. Phenolsulfonphthalein excretion was 55 per cent at the end of two hours.

The Mazzini test was negative.

Fasting blood sugar was 83 mg. per cent. The glucose tolerance test gave the following results: fasting, 68; 30 min., 130; 60 min., 160; 120 min., 108; 180 min., 83.

Sodium was 140 mEq./L, potassium 4.6 mEq./L; carbon dioxide 21.9 mEq./L; radioactive iodine uptake 17 per cent; cholesterol 214 mg. per cent; total protein was 6.7 gm. per cent; albumin 4.5 gm. per cent; globulin 2.2 gm. per cent; alkaline phosphatase 7.2 Bodansky units; calcium 6.7 mg. per cent, 6.3 mg. per cent; inorganic phosphorus 11.1 mg. per cent, 10.7 mg. per cent.

The electrocardiogram showed a Q-T interval prolonged to 0.44 seconds.

Lumbar puncture revealed an initial pressure of 130 mm. of water; 2 leukocytes; protein 42 mg. per cent; sugar 62 mg. per cent; calcium 4.5 mg. per cent; and inorganic phosphorus 1.8 mg. per cent.

The electroencephalogram (figure 2) showed a disorganized record with a good deal of poorly formed 4-6/second activity. In response to hyperventilation, high voltage 3/second wave activity in synchronous bursts was again seen within 20 seconds. There were no spike and wave groups on this occasion. The record was consistent with a convulsive disorder.

Psychometrics revealed an intelligence quotient of 70. The results were significantly lower in all areas tested when compared with previous examinations six months before.

X-rays of the hands, feet, and long bones revealed a definite widening of the medullary cavities of all the visualized bones. The cortices were definitely thinned and demineralized. There was no evidence of soft tissue ossification. The bone age was normal for a nine year old girl. The metacarpals (figure 3) were quite short, particularly the fourth and fifth on the right and the first on the left. The metatarsals showed the same general changes, but the lack of length was not as striking.

Roentgenograms of the skull demonstrated an increased thickness and granular character of the calvarium. No intracerebral calcification was noted.

Intravenous pyelogram showed mild bilateral megaloureters without caliectasis or pyelectasis. Bilateral coxa valga was also observed.

X-rays of the teeth revealed shortened root formation and poor development.

The Ellsworth Howard test gave the following results:

Patient

Time	Total phosphorus per 100 cc. of urine
1 to 2 hrs.	10.2 mg.
After 200 units of Parathormone intravenously	
3 to 4 hrs.	4.2 mg.
4 to 5 hrs.	6.1 mg.

Control Patient

Time	Total phosphorus per 100 cc. of urine
1 to 2 hrs.	5.8 mg.
After 200 units of Parathormone intravenously	
3 to 4 hrs.	12.7 mg.
4 to 5 hrs.	33.2 mg.

The results in the patient demonstrate a lack of phosphorus diuresis following the administration of intravenous Parathormone, and is typical of the response in pseudohypoparathyroidism.

Subsequent Course

The patient was observed for three weeks in the hospital while undergoing diagnostic studies. She was seizure free during this time but continued to complain of numbness and tingling in her hands and feet. Treatment for pseudohypoparathyroidism was started on August 8, 1954. This consisted of a low phosphorus diet plus daily administration of 3 cc. dihydrotachysterol, 100,000 units vitamin D, 12 gm. calcium lactate, and 60 cc. Amphogel in divided doses. The paresthesias disappeared from the extremities within four days. She was then discharged on the above regimen and followed at biweekly intervals in the clinic. Urine Sulkowitch test was performed daily at home. The Mysoline was discontinued upon discharge from the hospital.

By September 2, 1954 on the above therapy, serum calcium was increased 9.2 mg. per cent. The dihydrotachysterol was reduced to 1 cc. each day, the vitamin D to 50,000 units, and the calcium lactate to 6 gm. By October 7, 1954 the serum calcium had reached 10.5 mg. per cent where it has remained. Clinically, the patient showed considerable improvement. She has now been seizure free for a period of six months even though all anticonvulsant medication has been discontinued. Her mental picture has brightened considerably, with an increase in her intelligence quotient to 79 and some improvement in her electroencephalogram.

ANALYSIS OF CASES IN THE LITERATURE

Sex and Age Distribution

There appears to be a higher incidence of pseudohypoparathyroidism in

females. Of the 25 cases reported in the literature, 19 were female and only six were male. This is in contrast to idiopathic hypoparathyroidism where the sex distribution is about equal.[21] The earliest age at which the diagnosis of pseudohypoparathyroidism was established was three years and the latest 49 years.* The average age for the 25 cases was 20 years.

Of particular interest is the fact that an average of 14 years elapsed from the time evidence of the disease was present to the time of correct diagnosis. Many of the patients had been treated with various anticonvulsants for a number of years without improvement. It was apparent, in most cases, that the disease had been present long before symptoms of tetany or convulsions occurred. Although historical data are lacking in many instances, it can be inferred that stigmata of the disease were frequently present even at birth or within the first year of life.

Symptoms

The symptoms for which medical attention was sought were in almost all cases those secondary to the hypocalcemia. These ranged from mild degrees of paresthesias in the extremities, to muscle cramps, laryngospasm, carpopedal spasm, and generalized convulsions. In one patient (case 9) the major complaint was excessive sleepiness during the day time without any symptoms of accompanying tetany or convulsions.

Frank convulsions were described in 16 cases. The age at onset of convulsions varied from two weeks to 18 years. For the most part, they were typically grand mal attacks. Seizure-free intervals of several years' duration were not uncommon. In at least three of the patients, the convulsions were focal in nature, being confined to or more prominent on one side of the body. In the present case report, the majority of the attacks began in the right arm with spread to the right leg and only occasionally to the left side of the body. Following the attack, weakness of the right arm and leg lasting for several days was frequently present.

Physical Findings

In 24 cases it was either specifically mentioned or inferred that the patient was of shorter stature than average for the age. In association with the short stature, in most cases, the patients were described as having a full, round facies, short neck, and a thick, broad figure. Actual obesity was frequently stated to be present. In several instances, it was mentioned that these physical characteristics had been present since birth or shortly thereafter. The 49 year old male reported by Alexander and associates[3] weighed 45 pounds at nine months of age. Several other patients were reported as failing to lose their infantile fatness. Some degree of hypertelorism was reported in three patients, and examination of photographs in many of the other cases revealed the eyes to be set rather widely apart.

Another striking physical feature in pseudohypoparathyroidism is an abnormal shortening of one or several of the fingers and toes, usually more marked in the fingers. In 13 of the 25 cases, specific mention was made that at least one of the fingers was abnormally short. In addition to being short, the fingers were

*Since the preparation of this paper, the authors have had an opportunity to observe another case of pseudohypoparathyroidism in a seven week old baby girl who had a complicating subdural hematoma.

TABLE 1. PERTINENT FINDINGS IN 25 CASES OF PSEUDOHYPOPARATHYROIDSIM

Case	Author	Sex	Age	Duration of Symptoms Years	Symptoms	Physical Signs	Ca mg.%	P mg.%	X-ray Findings	Therapy and Results	Family Traits
1.	Albright, et al.	F	28	16	Seizures.	Short, round face. Mental retardation. Poor dentition. Short fingers.	6.4	6.2	Short metacarpals and metatarsals. Soft tissue calcification. Increased bone density. Thick skull.	Calcium to normal on A.T.-10. Decrease in seizures.	Sister had seizures, but calcium normal.
2.		F	12	9	Tetany. No seizures.	Short, round face. Mental retardation. Poor dentition.	8.9	6.3	Increased bone density.	A.T.-10. Tetany disappeared.	
3.		M	3	1	Choking spells. Seizures.	Short, round face. Soft tissue calcification.	7.1	10.0	Soft tissue calcification	Large doses A.T.-10. Tetany disappeared.	
4.	Sprague, et al.	F	33	14	Seizures.	Short, round face. Soft tissue calcification. Short fingers.	4.6	5.9	Short metacarpals. Calcium in basal ganglia and other soft tissues.	Improved on both A.T.-10 and calciferol.	
5.	Alexander, et al.	M	49	48	Seizures.	Short, round face. Soft tissue calcification. Cataracts. Poor dentition. Tremor. Shuffling gait.	6.8	4.5	Calcium in basal ganglia and other soft tissues. Osteoporosis.	Calcium to normal on A.T.-10 and calciferol. Felt better.	
6.	Peterman and Garvey	F	12	10	Hunger, hoarse voice.	Short, round face. Mental retardation. Soft tissue calcification. Poor dentition. Depressed reflexes.	6.6	11.0	Calcium in basal ganglia and other soft tissue. Osteoporosis. Spur on tibia.	Calcium to normal on A.T.-10. Seizures less frequent. Mentally improved.	
7.	Selye	F	8		Seizures.	Short, round face. Short fingers.	4.5	10.2	Short metacarpals. Soft tissue calcification. Osteoporosis. Spur on tibia.	Calcium to normal on A.T.-10. EEG improved.	
8.		F	8			Short, round face. Short fingers.			Short metacarpals.		Mother had short fingers.
9.	Schübach and Courvoisier	M	40			Short, round face. Mental retardation. Short fingers. Cataracts. Poor dentition.	4.3	4.2	Short metacarpals. Calcium in basal ganglia. Increased bone density. Thick tibial shaft.	A.T.-10. Improved.	
10.	Moehlig and Gerisch	F	19	8	Seizures.	Short, round face. Poor dentition.	4.7	9.3	Increased bone density.		Both parents short in stature.
11.	Bakwin, et al.	F	16	8	Seizures.	Short, round face. Mental retardation. Short fingers. Poor dentition. Depressed reflexes.	8.4	7.0	Short metacarpals. Osteoporosis. Thick skull. Bowing of ulna and radius.	A.T.-10. Calcium to normal. Improved.	Mother very short.
12.	Elrich, et al.	M	27	15	Seizures.	Short, round face. Mental retardation. Cataracts.	6.5	10.5	Calcium in basal ganglia.	A.T.-10. Calcium to normal. Seizures abolished	
13.		F	17	12	Increased sleepiness.	Short, round face. Mental retardation. Short fingers and toes.	5.8	5.2	Short metacarpals and metatarsals. Soft tissue calcification.		
14.		F	34	29	Tetany.	Short, round face. BP 190/115. Slight blurring of disk margins.	7.7	4.3	Calcium in basal ganglia.		Twin sister had tetany and calcium in basal ganglia.
15.		F	9	5	Tetany.	Short, round face.	4.8	9.2	Osteoporosis.	A.T.-10. Seizures abolished. Calcium to normal	
16.	Bishop and De Mowbray	F	18	12	Tetany.	Short, round face. Short fingers and toes. Poor dentition.	6.0	4.3	Short metacarpals and metatarsals. Calcium in basal ganglia and other soft tissues. Spur on tibia.	A.T.-10. Improved.	
17.	Zellweger and Girardet	F	10	10	Seizures.	Short, round face. Mental retardation. Depressed reflexes. Right Babinski. Short neck. Rough skin.	6.7	6.8	Calcium in soft tissues. Osteoporosis. Thick skull. Thick long bones.		
18.	Talbot	F	5	5	Tetany. Seizures.	Short, round face. Short fingers. Soft tissue calcification.	6.0	8.0	Short metacarpals. Soft tissue calcification.	Calcium to normal on A.T.-10. Spells relieved. Brighter.	Identical twin.
19.		F	5	5	Tetany. Seizures.	Short, round face. Short fingers. Soft tissue calcification.			Short metacarpals. Soft tissue calcification.	A.T.-10. Spells relieved. Brighter.	Identical twin.
20.	Reynolds, et al.	M	29	21	Stiffness. Jerking of legs.	Short, round face. Mental retardation. Short fingers. Soft tissue calcification. Cataracts. Poor dentition. Increased reflexes.	5.8	5.4	Short metacarpals. Calcium in basal ganglia and soft tissues. Osteoporosis. Thick skull. Thick long bones. Coxa vara.	Calcium to normal on A.T.-10. Spells relieved.	
21.	Wise and Hart	F	24	23	Seizures.	Short, round face. Mental retardation. Cataracts. Poor dentition. Blurred disks.	5.7	6.8	Calcium in basal g anglia. Increased bone density. Thick skull. Coxa valga.	Calcium to normal on A.T.-10. Spells relieved. EEG improved.	Sister had convulsions and died in infancy of ? cause.
22.	Bille	F	9	2	Seizures.	Short, round face. Mental retardation. Short fingers. Dry skin.	6.0	7.5	Short metacarpals. Osteoporosis.	A.T.-10. Improved	Maternal uncle was short and stocky. Imbecile.
23.	Martin, et al.	M	51	37	Tetany.	Mental retardation. Cataracts. Poor dentition.	7.0	4.2	Calcium in basal ganglia. Increased and decreased areas of bone density.		
24.	Ascrad, et al.	F	24	17	Seizures.	Short, round face. Cataracts. Poor dentition. Dry skin.	9.2	5.5	Soft tissue calcification. Increased and decreased areas of bone density.		Mother short. Sister died age 20. She had fits and resembled patient.
25.	Present case.	F	9	7	Seizures.	Short, round face. Short fingers and toes. Mental retardation. Depressed reflexes. Blurring of left disk. Poor dentition.	6.7	11.1	Short metacarpals and metatarsals. Osteoporosis. Thick long bones. Coxa valga. Megalo-ureter. Thick granular skull.	A.T.-10. Vitamin D. Improved. Much brighter.	Mother short with round face. Calcium deposits about left shoulder. Maternal uncle had calcific bursitis of left hip.

often described as broad and stubby. Detection of an abnormally short metacarpal bone on physical examination is best demonstrated by inspection of the dorsal surface of the clenched fist.[22] In three of the cases, abnormally shortened toes were present in addition to the shortened fingers.

The presence of palpable subcutaneous ossification is another feature that should suggest the possibility of pseudohypoparathyroidism. In seven of the 25 cases, subcutaneous nodules and plaques of calcium were noted. There seemed to be no particular site of predilection, as each major area of the body except the head was involved at least once. In two patients[12] subcutaneous ossification was noted at birth, while in other cases it appeared much later in life. In six cases, x-rays demonstrated soft tissue ossification in bursa and muscle that was not detected on physical examination. Thus a total of 13 out of 25 patients had evidence of soft tissue ossification, excluding the basal ganglia.

The majority of additional abnormal physical findings were those frequently seen in idiopathic hypoparathyroidism. Cataracts were mentioned in seven of the 25 cases with pseudohypoparathyroidism. However, careful ophthalmologic examination to detect early lens opacities was not done in every instance. Evidence of poor dentition characterized by defective eruption was present in 13 cases. Dryness and coarseness of the skin was present in three cases. Evidence of superficial fungus infections of the skin, which is sometimes found in idiopathic hypoparathyroidism, was not mentioned in any of the present cases reviewed.

The presence of mental retardation was specifically mentioned in 13 cases, and the average intelligence quotient was 72. In several patients there was evidence that mental retardation and slow physical development had been present since infancy. The mental retardation antedated the onset of seizures in a number of instances.

The present patient exhibited the characteristic physical appearance of pseudohypoparathyroidism. Indeed, it was the physical appearance accompanied by the refractory convulsive state that first suggested the diagnosis. The lack of soft tissue ossification in this patient emphasizes the variability of the clinical picture.

There was little information offered regarding neurologic examinations. Slight blurring of the disk margins was mentioned in three cases, but in these patients there was no additional evidence of increased intracranial pressure. The condition of the reflexes was mentioned in only five cases. In four, they were reported as depressed and in one as increased. In the present patient they were quite markedly depressed throughout. In two patients there was evidence of an abnormal plantar response.

A positive Chvostek was recorded in 17 cases and a positive Trousseau in 12 cases. In two patients, both the Chvostek and Trousseau responses were noted to be absent despite the presence of a low serum calcium.

Of special neurologic interest was the 49 year old male reported by Alexander and associates[3] in whom there was a typical parkinsonian gait and tremor. In this case one wonders if the cerebral calcification near the basal ganglia played a role in its pathogenesis.

Laboratory Data

Examination of the urine and routine

25.	Present case.	F	9	7	Seizures.	Short, round face. Short fingers and toes. Mental retardation. Defective enamel. Blurring of left optic disk margin.	6.7	11.1	Short metacarpals and metatarsals. Osteoporosis. Thick long bones. Cortex of mandible wider. Thick granular skull.

Mother aged 28 with round face, short fingers and toes. Pain in left shoulder. Maternal uncle had cubitis bursitis of left hip.

ACT-10. Vitamin D. Improved. Much brighter.

blood counts were unremarkable in most cases. In those cases tested, the urine Sulkowitch was negative. The average serum calcium level before the treatment was 6.8 mg. per cent with a range from 4.3 mg. per cent to 9.2 mg. per cent. The serum inorganic phosphorus ranged from 4.2 mg. per cent to 11.1 mg. per cent with an average of 7.5 mg. per cent. These values are similar to those found in idiopathic hypoparathyroidism.[21] When one considers the higher normal values found in children, the alkaline phosphatase determinations were either normal or only slightly elevated.

In 14 of the cases, tests of thyroid function were obtained. The round, full facies and mental dullness of patients with pseudohypoparathyroidism may suggest an element of hypothyroidism. In none of the cases, however, was there any convincing evidence of thyroid dysfunction. Determinations of the urine 17-ketosteroids were reported in four patients and were not remarkable.

There were six patients who had glucose tolerance tests. In two, there was evidence of impaired glucose utilization while in another the five-hour glucose tolerance test was flat. Serum electrolytes were obtained in only a few instances, and none showed any abnormality. In seven cases in which an electrocardiogram was obtained there was prolongation of the Q-T interval thought to be related to the associated hypocalcemia.

The results of cerebral spinal fluid examinations were mentioned in eight cases. In one patient the spinal fluid pressure was elevated to 290 mm., but there were no other signs of increased intracranial pressure present. The remainder of the spinal fluid examination was reported to be within normal limits. In the present patient the spinal fluid calcium of 4.5 mg. per cent and inorganic phosphorus of 1.5 mg. per cent were considered to be normal.[23]

Roentgenographic abnormalities are of considerable interest in pseudohypoparathyroidism and may involve the entire skeleton. It is well known that in idiopathic hypoparathyroidism there is usually an increased density of the bones.[24] In the present study five cases showed some degree of localized or generalized increased bony density, while seven cases demonstrated evidence of skeletal demineralization. In two patients there were areas of increased density as well as of decreased density. In the present patient, the generalized bony decalcification was quite striking.

The abnormal shortening of the fingers and toes is best demonstrated by roentgenogram. This finding occurred in 13 of the 25 cases. It is probably due to an early closure of the epiphyses of the metacarpal and metatarsal bones. In addition to being short, these bones may be quite thick and deformed. In several of the cases the phalanges were also reported as broad and distorted.

There was evidence that the long bones of the skeleton may show similar involvement. In nine cases, roentgenograms of the long bones were reported to show abnormalities. These consisted of widening of the medullary cavities in five patients, spur formation on the tibia in two patients, and bowing of the fibula in one patient. Two of the patients showed coxa valga and one coxa vara. The cranial vault in six patients was reported to be thick and granular in character. In several of the patients, x-rays of the teeth revealed shortened and defective root formation.

In 18 cases there was roentgenographic

evidence of soft tissue ossifications observed in the basal ganglia, muscle, ligaments, tendons, bursa, and subcutaneous tissues. Cerebral calcifications occurred alone in five cases, while extracerebral soft tissue ossifications were found alone in eight patients. In only five cases were cerebral calcifications and extracerebral soft tissue ossifications found together in the same patient. In seven cases, as far as could be determined, there was an absence of both ectopic ossifications and cerebral calcifications.

Five patients had intravenous pyelograms. Four were considered to be normal. The fifth, the patient described here, showed bilateral megaloureters without evidence of caliectasis or pyelectasis. Normal renal function ruled out the possibility that the metabolic disorder was secondary to any of the usual forms of renal insufficiency.

Pretreatment electroencephalograms were recorded in 12 patients. Two of the tracings failed to demonstrate any diagnostic abnormality. In the remaining ten patients the tracings were compatible with a diagnosis of convulsive disorder. In two of the patients the electroencephalogram was reported to show an improvement after the correction of the abnormally low serum calcium, as was the case in our patient. In another patient (case 1), however, the correction of the low serum calcium did not result in an improvement of the electroencephalogram.

Response to Parathorhome

One of the important differences between the idiopathic and pseudo forms of hypoparathyroidism is the difference in response to intravenous Parathormone. The Ellsworth-Howard test[25] demonstrates this very well. The original test has been modified somewhat.

To perform the Ellsworth-Howard test, the total urinary phosphorous excretion is determined hourly for three hours before and three hours after the intravenous administration of 200 units of Parathormone. A control patient to check the potency of the Parathormone should be tested.

According to Albright,[26] normal individuals respond to parathyroid hormone with a moderate (about three to fourfold) phosphate diuresis. In contrast, patients with pseudohypoparathyroidism usually show little or no response – usually less than a twofold response. Patients with idiopathic hypoparathyroidism will exhibit either a normal or greater than normal (up to sixfold) phosphate diuresis after 200 units of parathyroid hormone. It is difficult to compare the results of Parathormone response in the patients under discussion, because of the different doses of parathyroid extract used and individual variations of the method. It should be remembered that previous parathyroid administration may render a patient insensitive to subsequent parathyroid injections.

The specificity of the intravenous Parathormone test for pseudohypoparathyroidism is open to some question. In at least two cases (6 and 9) of the present series, there was a phosphorus diuresis greater than one would expect in a patient with pseudohypoparathyroidism. These cases, however, had the typical physical characteristics of the syndrome. Albright's group[9] is of the opinion that the response to intravenous Parathormone may not be reliable in all instances to differentiate between the pseudo and idiopathic forms of hypoparathyroidism.

Conversely, it is not known for certain whether an intravenous Parathormone test compatible with pseudohypoparathyroidism is always indicative of this entity, even in the absence of characteristic physical findings. This question was raised by the case of a 74 year old male patient with Parkinson's syndrome observed by the authors. This patient was admitted to the Presbyterian Hospital for observation of possible myocardial infarction. Because of cataracts, serum calcium was determined and found to be 6 mg. per cent. Serum inorganic phosphorus was 5.8 mg. per cent and alkaline phosphatase 2 Bodansky units. After the intravenous injection of 200 units of Parathormone, there was essentially no increase in the urinary phosphorous excretion, a result which was compatible with pseudohypoparathyroidism. However, the height and facies were normal, there was no soft tissue ossification, and roentgenograms of the skull, hands, and feet were normal. Thus, the lack of apparent response to intravenous Parathormone and the lowered serum calcium were the only findings that suggested pseudohypoparathyroidism.

Therapy and Response

Statements regarding treatment and response were recorded in 18 of the 25 cases. The mainstay of the initial therapy in all cases was dihydrotachysterol. The initial dose was 1 to 3 cc. per day, in most cases supplemented by calcium salts and 25,000 to 100,000 units of vitamin D. All of the patients appeared to have some symptomatic improvement. This was manifested by a decrease or a complete disappearance of the tetany and convulsions. In three patients it was noted that the attention span and mental picture improved after treatment.

In our patient the response to treatment was gratifying. She has been seizure free for six months and is more outgoing and alert. There has been a gain of nine points in her intelligence quotient, but of greater importance is the fact that her school work is much better. Her mental status is continuing to improve.

In all cases the clinical improvement was accompanied by a return of the serum calcium to normal. In many cases, as the serum calcium returned to normal, slightly larger doses of vitamin D were successfully substituted for the more expensive dihydrotachysterol. Dangerous hypercalcemia was guarded against by a close check on the urine Sulkowitch reaction and occasional serum calcium determinations. In no case was there any evidence of improvement in the abnormal physical characteristics. In one patient,[4] follow-up roentgenograms after treatment showed an increase in the soft tissue ossification.

Evidence of Heredity

In 11 of the 25 cases there was evidence that other members of the family exhibited some traits present in the patients with pseudohypoparathyroidism. Of 14 close relatives having suggestive traits, 11 were in females, again suggesting the apparent feminine predominance. The presence of a short stature was noted in the mothers of four patients and in the father of one patient. One mother exhibited short metacarpals and bowing of the radius. Two of the patients reported[12] were twin sisters. Another patient (case 3),[9] had a twin sister with tetany as well as calcium deposits in the basal ganglia. The patient reported by Azerad et al.[17] had a

sister who resembled her in appearance and who also had convulsions and cataracts. The sister died at age 20 of unknown causes.

In the present case the patient's mother was only five feet tall and had a full round facies very similar to that of the patient. She demonstrated soft tissue ossifications, but no abnormal shortening of the metacarpals. Her serum calcium was within normal limits.

From the evidence presented it would appear that the genetic relationship is closer in the pseudo than in the idiopathic form of hypoparathyroidism.[21]

Diagnosis

As more cases of pseudohypoparathyroidism are reported, the variability of the clinical picture becomes evident. A typical patient, usually female, might present with symptoms of tetany and convulsions. On physical examination she would be of short stature with a full, round facies and broad figure. One or several of the fingers and toes would be abnormally short, and there would be noticeable soft tissue ossifications. There would be evidence of some mental retardation. Serum calcium would be depressed and serum inorganic phosphorus elevated. If, in addition, there was little or no increase in urinary phosphorous excretion after 200 units of intravenous Parathormone, the diagnosis of pseudohypoparathyroidism would seem fairly certain.

It is likely, however, that most patients with pseudohypoparathyroidism will be lacking in one or more of the above features. For instance, the fingers may be of normal length and there may be an absence of soft tissue ossifications. In an occasional case there may be a normal phosphorous diuresis after 200 units of intravenous Parathormone. In this instance, however, the physical characteristics of the syndrome should be present associated with a depressed serum calcium.

The differential diagnosis of pseudohypoparathyroidism may include a large number of disorders. Rickets, renal insufficiency, and steatorrhea can all produce a lowered serum calcium. A past history of thyroid surgery will suggest the possibility of operative damage to the parathyroid glands as the cause of hypocalcemia.

Idiopathic hypoparathyroidism presents probably the most difficult and important differential diagnostic problem. Here the symptomatology and chemical derangements are similar to those of pseudohypoparathyroidism. Even many of the physical findings, such as cataracts, poor dentition, and mental and physical retardation are present in both entities. However, in pseudohypoparathyroidism the characteristic facies and stature, when associated with abnormally shortened digits and soft tissue ossification, are distinctive. In addition, the effect of 200 units of intravenous Parathormone on the urinary phosphorus excretion should in most cases demonstrate a clearcut difference in response. As final proof of the presence of pseudohypoparathyroidism, normal parathyroid tissue should be demonstrated by biopsy.

Other causes of tetany and convulsive disorders will enter into the differential diagnosis. The tetany of hyperventilation, alkali ingestion, and that from excessive loss of gastric contents through vomiting will be readily explained. Pseudohypoparathyroidism should be considered in all convulsive disorders when other metabolic and specific causes have

been ruled out. In particular it should be considered in those patients diagnosed as having idiopathic epilepsy. This is especially true if these patients are refractory to the usual anticonvulsant medications.

In the present patient, as well as in several of the reported cases, the possibility of a brain tumor was considered to the point of carrying out pneumoencephalography and arteriography. Findings that raised the question of brain tumor were cerebral calcifications, refractory convulsions sometimes focal in nature, and blurred disk margins suggesting papilledema.

Pseudohypoparathyroidism should be considered in patients with dwarfism, especially achondroplasia, and mental retardation. The obesity, round face, and mental sluggishness that characterize patients with pseudohypoparathyroidism will in many cases suggest the presence of hypothyroidism. Myositis ossificans progressiva, in which there are shortened digits and soft tissue calcifications, may at first be confused with pseudohypoparathyroidism. In the former entity, the calcifications are painful in contrast to those seen in pseudohypoparathyroidism and the serum calcium is normal.

More recently Albright and his associates[22] have reported a patient with what they call pseudo-pseudo-hypoparathyroidism. The patient was an adult woman with all the physical characteristics of pseudohypoparathyroidism as well as a compatible intravenous Parathormone test. The serum calcium and inorganic phosphorus, however, were within normal limits. Undoubtedly further variations will be reported in the future. It might be particularly rewarding to look for such variants in family members of patients with pseudohypoparathyroidism.

Etiology

Albright's original explanation of pseudohypoparathyroidism still appears to fit the known facts of the syndrome. There is apparently no lack of parathyroid hormone in these patients. Parathyroid biopsies have been reported in at least four cases and were found to be either normal or hyperplastic. This suggests, but does not prove, the secretion of a normal amount of parathyroid hormone. The failure of patients with pseudohypoparathyroidism to exhibit a normal phosphorous diuresis after 200 units of intravenous Parathormone suggests inability of the kidney tubules to respond fully to the parathyroid hormone. In other words, there appears to be a failure of end-organ response rather than a lack of hormone.

On the other hand, the recent work of Steward and Brown[27] suggests that the activity of endogenously produced parathyroid extract is not entirely contingent on kidney function. In addition, these same authors found a significant phosphorous diuresis in dogs after the injection of inactivated Parathormone, as well as after spleen and thymus extracts. Neither of these observations, however, disproves that Parathormone causes a phosphorous diuresis by its action on the kidney tubules. It is conceivable that Parathormone may have two sites of action, one the bone and the other the kidney tubules.

The failure to respond to intravenous Parathormone would seem to explain only part of the entire picture. Equally important are the accompanying characteristic physical findings which may be unrelated to the failure to respond to

intravenous Parathormone. The family history in many of the patients with pseudohypoparathyroidism is suggestive of a genetic disturbance. It may be, as suggested by Bishop and DeMowbray,[10] that any one of the major components of pseudohypoparathyroidism may be inherited independently of the others. It would seem reasonable to conclude, on the basis of present evidence, that pseudohypoparathyroidism is hereditary rather than acquired.

SUMMARY AND CONCLUSIONS

1. A clinical review of 25 cases of pseudohypoparathyroidism has been presented. Twenty-four cases have been collected from the world literature and an additional case is reported in detail. Nineteen of the 25 patients reported are females. The youngest patient reported is three years of age, and the oldest is 49 years.

2. The usual presenting symptoms in pseudohypoparathyroidism are tetany and convulsions.

3. The more common physical characteristics of the syndrome are a short stature, round facies, cataracts, poor dentition, mental dullness, abnormally shortened digits, and ectopic calcifications.

4. The outstanding laboratory abnormalities are a depressed serum calcium and elevated serum inorganic phosphorus. In addition, a twofold phosphorous diuresis or less following the administration of 200 units of intravenous Parathormone is almost pathognomonic of pseudohypoparathyroidism.

5. The family histories suggest that there may be a genetic tendency in many of the patients with pseudohypoparathyroidism.

6. The pathogenesis of pseudohypoparathyroidism is considered to be a failure of the end organ to respond to circulating parathyroid hormone.

7. Significant symptomatic improvement can be expected to result from proper therapy including dihydrotachysterol and vitamin D.

8. Pseudohypoparathyroidism should be considered in the differential diagnosis of convulsive disorders.

The authors wish to thank Dr. Fuller Albright for his critical appraisal of the manuscript and for his many constructive suggestions.

REFERENCES

1. Albright, F., Burnett, C. H., Smith, P. H., and Parson, W.: Pseudohypoparathyroidism; an example of "Seabright-Bantam syndrome". Report of 3 cases, Endocrinology 30:922, 1942.
2. Sprague, R. G., Haines, S. F., and Power, M. H.: Metabolic effects of parathyroid hormone, dihydrotachysterol and calciferol in a case of pseudohypoparathyroidism, J. Lab. & Clin. Med. 30: 363, 1945.
3. Alexander, S. B., and Tucker, H. St. G., Jr.: Pseudohypoparathyroidism: Report of a case with late manifestations, J. Clin. Endocrinol. 9:862, 1949.
4. Peterman, M. G., and Garvey, J. L.: Pseudohypoparathyroidism, Pediatrics 4:790, 1949.
5. Selye, H.: Textbook of Endocrinology. Montreal, Acta Endocrinologica Inc., 1949. 570 pp.
6. Schüpback, A., and Courvoisier, B.: Existe-t-il un pseudohypoparathyroidism?, Schweiz. med. Wchnschr. 79:887, 1949.
7. Moehlig, R. C., and Gerisch, R. A.: Pseudohypoparathyroidism with decreased glucose tolerance. Report of a case, J. Clin. Endocrinol. 10: 1609, 1950.
8. Bakwin, H., Gorman, W. F., and Ziegra, S. R.: Pseudohypoparathyroid tetany, J. Pediat. 36:567, 1950.
9. Elrick, H., Albright, F., Bartter, F. C., Forbes, A. P., and Reeves, J. D.: Further studies of pseudohypoparathyroidism; report of 4 new cases, Acta endocrinol. 5:199, 1950.
10. Bishop, P. M. F., and DeMowbray, R. R.: Pseudohypoparathyroidism, Proc. Roy. Soc. Med. 44: 952, 1951.
11. Zellweger, Von H., and Girardet, P.: Zur Problematik des Pseudo-hypoparathyreoidismus und des hypoparathyreotischen Kretinismus, Helvet. paediat. acta 6:184, 1951.
12. Talbot, N. B., Sobel, E. H., McArthur, J. W., and Crawford, J. D.: Functional Endocrinology

From Birth Through Adolescence, Cambridge, Harvard University Press, 1952. 113 pp.

13. Reynolds, T. B., Jacobson, G., Edmondson, H. H., Martin, H. E., and Nelson, C. H.: Pseudohypoparathyroidism; report of a case showing bony demineralization, J. Clin. Endocrinol. 12:560, 1952.
14. Wise, B. L., and Hart, J. C.: Idiopathic hypoparathyroidism and pseudohypoparathyroidism, Arch. Neurol. & Psychiat. 68:78, 1952.
15. Bille, Bo, S. U.: Pseudohypoparathyroidism, Acta paediat. 41:380, 1952.
16. Martin, E., Guye, P., Babel, J., and Courvoisier, B.: Tetanie idiopathique et pseudohypoparathyroidisme, Ann. endocrinol. 13:943, 1952.
17. Azerad, E., Gatha, J., and Raverdy, P.: Un cas de pseudo hypoparathyroidisme, Societe Medicale des Hopitaux de Paris 69:119, 1953.
18. Lowe, C. U., Ellinger, A. J., Wright, W. S., and Stauffer, H. M.: Pseudohypoparathyroidism (the Seabright Bantam syndrome), J. Pediat. 36: 1, 1950.
19. Berardinelli, W.: Pseudohypoparathyroidism with decreased glucose tolerance and diabetes insipidus, Acta endocrinol. 7:7, 1951.
20. Lachman, A.: Hypoparathyroidism in Denmark; clinical study, case 59, Acta med. scandinav. supp. 121:1, 1941.
21. Steinberg, H., and Waldron, B. R.: Idiopathic hypoparathyroidism; an analysis of 52 cases including the report of a new case, Medicine 31: 133, 1952.
22. Albright, F., Forbes, A. P., and Henneman, P. H.: Pseudo-pseudo-hypoparathyroidism, Tr. A. Am. Physicians 65:337, 1952.
23. Merritt, H. H., Mettler, F. A., and Putnam, T. J.: Fundamentals of Clinical Neurology, Philadelphia, Blakiston Co., 1947. 327 pp.
24. Albright, F., and Reifenstein, E. C.: The Parathyroid Glands and Metabolic Bone Diseases, Baltimore, Williams & Wilkins Co., 1948. 32 pp.
25. Ellsworth, R., and Howard, J. E.: Studies on physiology of the parathyroid glands. Some responses of normal human kidneys and blood to intravenous parathyroid extract, Bull. Johns Hopkins Hosp. 55:296, 1934.
26. Albright, Fuller: Personal communication.
27. Stewart, G. S., and Brown, H. F.: The urinary phosphate excretion factor of parathyroid gland extracts; a hormone or an artefact? Endocrinol. 51:80, 1952.

■ But, if Sir Charles Bell's views concerning the roots of nerves are now based upon irrefragable experiments, it is not so as regards either of the views that he successively proposed concerning the columns of the spinal cord. We will prove by anatomical, experimental, and pathological facts, that his ideas concerning the channels for sensation and volition are not exact. But, at the same time, that we show the mistakes he has committed in this respect, we will bring forward a great many proofs of a theory of this eminent physiologist, which is by far of greater importance than the views he held respecting the place of passage of the sensitive impressions, and the orders of the will in the spinal cord. The great theory of Sir Charles Bell was, not that volition and sensation have their conductors in this or that place, but that these conductors are distinct one from the other, all along from the brain to the periphery. It is this principle of a complete distinction between the elements of the nerves and of the spinal cord, which are employed in motion and in sensation, which is the great thing that science particularly owes to him. Others had had this idea, but no one so powerfully as he had; and, also, no one tried to prove it, as he did. But, the principle being imagined, it remained to find out, first, positive proofs of its existence; and, secondly, whether the conductors — though distinct one from the other, are congregated together in the same sheath (as in the trunks of the spinal nerves), or are separated in distinct bundles, as they seem to be in the roots of the spinal nerves.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Pathogenesis of Ophthalmoplegic Migraine

Adrien Ver Brugghen, M.B., Ch.M., M.S.

OPHTHALMOLOGISTS AND NEUROLOGISTS are on the alert for symptoms of an intracranial aneurysm. Since the current impetus to arteriographic study of intracranial vessels, hitherto unsatisfactorily explained ocular phenomena have been found to be associated with changes in blood vessels. In many cases "silent" ocular palsies have been shown to be due to aneurysm of the circle of Willis.

The most frequent and characteristic ocular symptom is that of oculomotor palsy, with its clearly noticeable ptosis. On questioning patients showing such a condition, the "silence" is perhaps not conspicuous; in fact, many patients have associated headache on the affected side and others have, in addition, numbness of the ophthalmic division of the trigeminal nerve. Certainly a patient presenting such a picture today would be subjected to bilateral arteriography without delay. In the vast majority an aneurysm would be found and, without some form of surgical treatment, aneurysmal rupture would eventually take place. No one would argue about the relationship of the aneurysm to the oculomotor palsy, or the relationship of the headache to the aneurysm. Some rare cases of aneurysm are said to have produced recurrent, in a limited sense, attacks of ocular palsy with ipsilateral headache. Exceptionally, oculomotor palsy has been found to be due to some other cause, such as tumor of the nerve itself or tuberculous involvement of the nerve.

There is also an exceptional case in which there are repeated attacks of nausea and vomiting, with unilateral headache followed by oculomotor palsy on the same side. Time, repeated arteriography, exploration, and even autopsy have failed to reveal an aneurysm or any other demonstrable cause for the unilateral oculomotor palsy. Such cases are known as ophthalmoplegic migraine. They must be distinguished from cases of oculomotor palsy with headache in a patient who might harbor a tumor or an aneurysm, and in whom the criteria for a diagnosis of migraine would be missing. In brief, the criteria are recurring attacks of generalized or localized headache lasting a few minutes to a few hours, with nausea and vomiting.

Instances of ophthalmoplegic migraine are quite rare in the English literature, and formerly the only proved cases were those followed for a long period of time which finally came to autopsy. More recently there have been five easily ac-

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cessible cases, two of Alpers and Yaskin,[1] one of Ford,[2] one of Woodhall,[3] and one described by Walshe.[4] Before the advent of the general use of arteriography, the diagnosis of ophthalmoplegic migraine was treated with the utmost skepticism. As recently as 1946 a group of eminent neurologists so expressed themselves.[5] That the skepticism is ingrained is still evident as shown by the two authentic cases of Alpers and Yaskin.[1] In one of these exploration was carried out in spite of a negative arteriogram. Postmortem examination at a later date failed to disclose a lesion which could be held responsible for the recurring attacks of hemicrania with ophthalmoplegia. Ford described a case with recurring symptoms and signs for 13 years, starting at the age of three.[2] Walshe's case started having symptoms at 13 years of age and was examined again when he was 47 years old.[4] Neither of these cases had an arteriogram, but the time factor is significant and tumor or aneurysm as causes of the condition are highly improbable. In Woodhall's case,[3] quoted by Ford, a 10 year old girl had recurring attacks with complete recovery, with the first episode when she was one year old; ventriculograms and arteriograms were negative. The present status of the cases of Ford and of Woodhall could not be ascertained at the present time.[6] The case reported here concerns an eight year old girl with repeated attacks of headache, vomiting, and internal and external ophthalmoplegia. There have been four spaced negative arteriographic studies. There is now a permanent internal and partial external ophthalmoplegia.

CASE REPORT

A 12 year old girl was first seen at the Presbyterian Hospital of Chicago in 1943 at the age of 14 months, when the mother stated that the child had awakened with a drooping eyelid two days previously. There had been no crying or complaint of pain.

On examination there was a complete right external oculomotor nerve palsy with ptosis and external strabismus. The right pupillary reaction to light was normal, as was the consensual reaction. Both optic disks were normal. An ophthalmologist and pediatrician suggested a nuclear lesion or a peripheral neuritis. She was next seen by the author in May 1951 when she was eight years old. There had been recurring attacks of the ptosis and ophthalmoplegia about once a year. The history of the attack was that she had severe right frontal headache with nausea and vomiting on the day prior to the ocular symptoms, and when she woke up the following morning her right eye was in an abnormal condition. The right eyelid was closed, the eye was turned outward, and the pupil was dilated. The eye symptoms gradually cleared up in a month or six weeks so that for approximately ten months in the year her eyes appeared normal. The present episode had begun one month previously and there had been no improvement in the right eye.

On examination there was ptosis of the right eye, which was held in a position of lateral gaze. The pupil was widely dilated and showed no reaction to light or in accommodation. There was no change in the size of the pupil by consensual light stimulation nor with movements of the sound left eye. The corneal reflex was normal. The fields, visual acuity, and the fundi were normal. A routine neurologic examination was negative. She had been seeen a few days before by an ophthalmologist who suggested an aneurysm and proposed neurosurgical consultation. The patient was admitted to the hospital for arteriography. Roentgenograms of the skull were normal, and a Prostigmine test did not cause any improvement in the eye findings. The arteriogram suggested slight deformation at the junction of the posterior communicating artery and internal carotid arteries on the right. Repeated examination of these films and three other arteriograms failed to confirm this impression; these and subsequent films were later considered to be negative.

Four months later, in September 1951, there was another episode with similar ocular symptoms. Visual acuity, visual fields, and fundi

FIG. 1. Normal arteriogram, November 1952.
FIG. 2 and FIG. 3. Patient's appearance in March 1953, showing abnormal condition of right eye.
FIG. 4. The right pupil is fixed and smaller than the left before the flash of the camera.
FIG. 5. The right pupil does not respond to accommodation as does the left. The weakness of internal rotation on the right is apparent.

were normal. Spinal puncture was normal in every respect. The arteriogram was normal. The next admission was in November 1951; there had been two episodes of right-sided headache and vomiting without ocular symptoms. The present attack began four days before and was similar in every way to the others. An open right internal carotid and indirect vertebral arteriograms were done and the arteriograms were regarded as normal. In spite of this, and after a Matas test, the right internal carotid artery was gradually occluded with a clamp and the vessel was tied off.

Six months later the patient was admitted with right-sided headache, nausea, vomiting, and a complete third nerve palsy, and following this episode the pupil has not returned to normal size. There was an attack in August 1952 and another in February 1953. On this occasion a fourth and final arteriogram was done which failed to reveal a lesion. Spinal fluid findings were again normal. The four sets of arteriograms were reviewed in consultation with two neurosurgeons and were considered to be within normal limits.[7,8]

Close questioning of the parents revealed that both the father and his mother had attacks that were similar to those of the child

but without ocular phenomena. The accompanying photographs were taken in March 1953. At the present time, August 1954, the right pupil is dilated, does not respond to light, consensual stimulation, or ocular movements, and there is weakness of internal rotation in the right eye.

COMMENT

The prejudice against the diagnosis of ophthalmoplegic migraine led not only to four arteriograms but to the ligation of the right internal carotid artery. It is well known that not all aneurysms are revealed by arteriography,[9] and it has been the author's experience that repeated arteriography may reveal the lesion.

DISCUSSION

A full discussion of the term ophthalmoplegic migraine is quite involved. Migraine itself is difficult to explain and when combined, if it is, with ophthalmoplegia, it is still more complex. The classical description of migraine, or hemicrania, consists of recurring attacks of generalized or localized headache usually lasting a few hours and accompanied by nausea and vomiting. Sequelae are rarely seen.

Ophthalmic migraine includes the above description, with the addition of ocular phenomena in the field of vision only. These phenomena include scintillating scotomata and/or homonymous hemianopsia of short duration. This is really the classic migraine but it only occurs in a small percentage of cases, 10 per cent according to Riley.[10] Ophthalmoplegic migraine is probably still another particular form, with paralysis or paresis of the intraocular or extraocular muscles or both. To satisfy the criteria, the ocular phenomena should be associated with the hemicrania and nausea and vomiting in recurring bouts. In addition the patient should be followed to the point where a specific localized lesion can be virtually dismissed from the differential diagnosis. Ophthalmoplegic migraine is diagnosed by the exclusion of other possibilities.

The differential diagnosis concerns aneurysm, myasthenia gravis, progressive nuclear ophthalmoplegia, and possibly discrete tumor in the pons. The state of the pupil is important for it is normal in myasthenia gravis. When myasthenia gravis affects the eyelid and the extraocular muscle, a suitable test with Prostigmine should give some indication of improvement in muscle function. Progressive nuclear ophthalmoplegia is rare and usually there is a hereditary factor. Other forms of nuclear ophthalmoplegia are associated with vascular lesions or tumors of the brainstem. In rare instances, progressive muscular atrophy, multiple sclerosis, and intoxications must be considered. Injury may produce ophthalmoplegia. The history, accompanying neurologic signs, and the time element help to differentiate these from the recurrent bouts of ophthalmoplegia associated with nausea and vomiting.

The pathogenesis of migraine is not clear and there are many theories, none of which is entirely satisfactory. That there is no significant change in intracranial pressure both during and between attacks has been demonstrated.[11] The most widely held view today is that it is a functional disturbance of the blood vessels of the head in which the branches of the external carotid artery are implicated. There is a period of vasospasm followed by dilatation.[12] Though this view may be correct, it scarcely explains ophthalmic migraine, for in this form it would appear that the internal carotid artery is involved

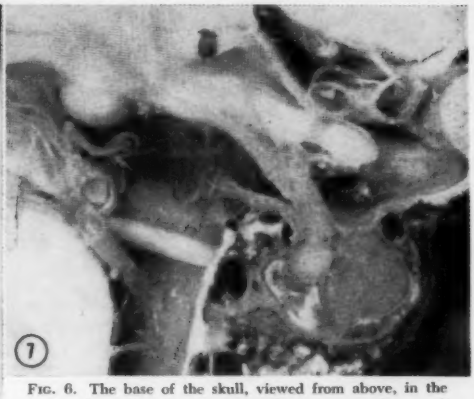

FIG. 6. The base of the skull, viewed from above, in the region about the pituitary fossa, the cavernous sinus, and the tentorial notch. The manner in which the third nerve crosses the tentorial gap and is related to the posterior cerebral artery, the posterior communicating artery, and the roof of the cavernous sinus is shown. From Sunderland and Bradley.

FIG. 7. A midsagittal section of the base of the skull illustrating how the third nerve crosses the tentorial gap and the manner in which it is sandwiched between the posterior cerebral and superior cerebellar arteries. From Sunderland and Bradley.

with interference with the visual cortex. This is supported by the scintillating scotomas commonly described and the homonymous hemianopsia found during the hemicrania. The difficulty of explanation is even greater in ophthalmoplegic migraine, and some consider that it is not migraine at all and they prefer to regard the condition as one of unilateral cephalgia with ophthalmoplegia.[13] This view is also difficult to accept, for in some cases in which no other pathologic process was ever found the characteristics of migraine were clear. The family history, the symptoms of the attacks, the periods of normality, the recurring bouts, the unilateral headache, and the gastrointestinal symptoms were repeatedly present. The only difference was the addition of transitory oculomotor symptoms. An attempt will be made later in this paper to bring opthalmoplegic migraine into line with the theory of contraction and dilatation of blood vessels. The blood vessels involved, however, are part of the internal carotid or the vertebral system or both.

The oculomotor symptoms may be bizarre. The paralysis is of the peripheral type.[14] The onset of external and internal ophthalmoplegia is rapid, but recovery is slow. The rate of recovery may be different for the internal and external ocular muscles. In prolonged cases such as the one described here, the internal and external muscles may not recover fully, leaving the individual without ptosis but with diplopia and with a permanently dilated pupil. This brings up two questions. What is it that injures the oculomotor nerve, and where is the lesion? Are the different parts of this small nerve more or less susceptible to injury? Certainly there is a difference in the recovery rate of the parts.

It is well known that the oculomotor

nerve is susceptible to injury, as can be seen in head injuries with and without clot formation over the convexities. The mechanism of injury without hematoma is usually interference with bony structures at the base or in the orbit.[15] That nerves may be involved in hematoma formation, either extra- or intradural, is a matter of common knowledge. The oculomotor findings have been produced experimentally in monkeys by introducing space-occupying material, which in turn caused hippocampal herniation with stretch or pressure on the nerve.[16] Paresis or paralysis of the nerve is a sign of great importance in expanding lesions of the hemispheres. The recovery of the nerve, especially the pupillary component, is a significant prognostic sign in extradural hemorrhage.[17] This type of dysfunction is fairly well understood, but it brings us little closer to a comprehension of the mechanism of third nerve disturbance in ophthalmoplegic migraine.

The ophthalmoplegia occurs on the same side as the migraine, although there need not be oculomotor phenomena with every attack. A more thorough appreciation of the anatomy of the nerve and a correlation of this with the current idea of the mechanism of migraine, with regard to contraction and dilation of cerebral blood vessels, may throw some light on the subject. The nerve, after it leaves the brainstem on its way to the cavernous sinus, is sandwiched between the posterior cerebral and superior cerebellar arteries. Arteries often show variations in origin, branching, and distribution. It is quite clear from figures 6 and 7 that with certain anatomic variations there could be actual compression or stretch of nerves crossing the tentorial gap. Sunderland made studies of the base of the brain during and following its removal from the cranial cavity in 210 dissecting room subjects.[18] Figures 8, 9, 10, and 11 show clearly that under certain conditions there is gross evidence of contact and compression of the oculomotor nerve by the internal carotid artery and parts of the circle of Willis.

As Sunderland says, "All that is claimed is that these observations demonstrate that, even when the normal arrangement obtains, large arteries are on occasion so related to nerves that they may press upon, displace, and deform them. In this way they could conceivably impair their function."[18] Unfortunately it was only rarely possible to correlate antemortem symptomatology with what was found in the dissecting room. There is plenty of evidence to demonstrate that nerves may be distorted and stretch with little or no evidence of disturbance of their function. It may well be that a sufficient degree of spasm and dilation of these vessels simultaneously may actually compress and indent the nerve.

The only questions to be answered are why certain parts of this small nerve are more affected than others, and why recovery is not more uniform in the whole nerve? Sunderland and Hughes have studied the pupilloconstrictor pathway in cadavers and found a concentration of finely myelinated fibers in the third nerve.[19] The finely myelinated fibers were those found to enter the ciliary ganglion and, in that part of the oculomotor nerve between the cavernous sinus and the brainstem, it could be assumed with reasonable certainty that these fibers lay at and around the superior surface of the nerve. From studies on extradural hemorrhage it is fairly

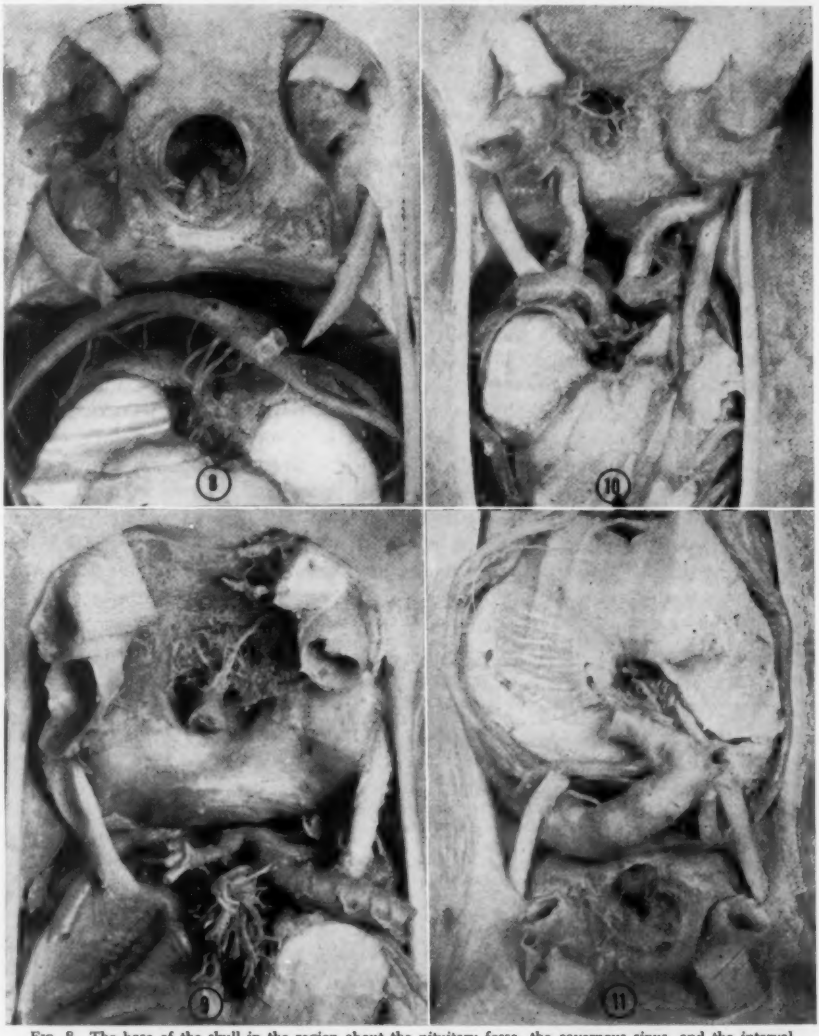

FIG. 8. The base of the skull in the region about the pituitary fossa, the cavernous sinus, and the interval between the brainstem and the dorsum sellae (from above). The posterior cerebral artery has been removed on the left side, exposing a deep groove extending into the upper surface of the third nerve. The groove was caused by the artery as it crossed and dragged on the nerve. From Sunderland.

FIG. 9. The base of the skull in the region about the pituitary fossa and cavernous sinus (from above). The left posterior cerebral artery, which branched from the internal carotid, has been removed thereby revealing the groove outlined by it on the upper surface of the oculomotor nerve. From Sunderland.

FIG. 10. The base of the skull in the region about the pituitary fossa, the cavernous sinus, and the interval between the brainstem and dorsum sellae (from above). The internal carotid artery and the posterior cerebral artery arising from it are shown pressing on the oculomotor nerve where that structure is coursing on the roof of the sinus preparatory to entering it. From Sunderland.

FIG. 11. The interval (from above) between the brainstem and the dorsum sellae, showing the basilar artery arching upwards to displace the right oculomotor nerve upwards and to the right. From Sunderland.

clear that the pupillary fibers are more susceptible to deformation than the somatic. It can also be shown that in extradural hematoma the pupillary fibers recover more quickly, and that the recovery of somatic components may be long delayed. The reason for the susceptibility of pupillary fibers is probably their exposed position in the nerve trunk.

There is every reason to believe that the observations mentioned are valid and that they can probably be applied to ophthalmoplegic migraine. The position of the nerve as it crosses the tentorial gap is such that it is liable, in certain individuals, to compressions and indentations by various intracranial arteries. All that is required to actually interfere with the function of the nerve is spasm, with distortion and traction, followed by dilatation. With the passing of the attack the nerve is again freed from the noxious pressure and functional recovery takes place. It also seems likely that repeated trauma to the oculomotor nerve, may ultimately lead to permanent damage. Such a case was reported by Wilson.[21]

The idea that ophthalmoplegic migraine is caused by blood vessels pressing on the oculomotor nerve during an attack of migraine is not new. It was first proposed by Bramwell[14] and later by Ehlers,[20] but probably received little support because it was regarded as a conjecture. The beautifully illustrated anatomic work of Sunderland and the clinical studies of Wolff fit together to make a strong argument for the pathogenesis of ophthalmoplegic migraine. This brings the phenomena observed into line with those commonly seen in aneurysms near the bifurcation of the internal carotid artery, which remain the most important probabilities in differential diagnosis.

REFERENCES

1. Alpers, B. J., and Yaskin, H. E.: Pathogenesis of ophthalmoplegic migraine, Arch. Ophth. 45:555, 1951.
2. Ford, F. R.: Diseases of the Nervous System in Infancy and Childhood, ed. 3, Springfield, Ill., Charles C Thomas, 1952, pp. 1062-1064.
3. Woodhall, B., quoted by Ford, F. R.: Diseases of the Nervous System in Infancy and Childhood, ed. 3, Springfield, Ill.: Charles C Thomas, 1952, p. 1062.
4. Walshe, F. B.: Clinical Neurophthalmology, Baltimore, The Williams & Wilkins Company, 1947.
5. Kennedy, F.: Discussion by Riley, H. A.: A case of ophthalmoplegic migraine and a theory for its production, J. Nerv. & Ment. Dis. 104:89, 1946.
6. Ford, F. R., and Woodhall, B.: Personal communication.
7. Sugar, Oscar: Personal communication.
8. Ecker, Arthur: Personal communication.
9. Hamby, W. B.: The aneurysmal origin of nonfatal subarachnoid hemorrhage, J. Neurosurg. 10: 35, 1953.
10. Riley, H. A.: Migraine, Bull. Neurol. Inst. New York 2:429, 1932.
11. Von Storch, T. J. C., and Merritt, H. H.: The cerebrospinal fluid during and between attacks of migraine headaches, Am. J. M. Sc. 190:226, 1935.
12. Wolff, H. G.: Headache in the migraine syndrome, in Headache and Other Head Pain, New York, Oxford University Press, 1948.
13. Donahue, H. C., Migraine and its ocular manifestations, Arch. Ophth. 43:96, 1950.
14. Bramwell, E.: Upon leaking aneurysm of the cerebral arteries as cause of third nerve paralysis, with special reference to 2 cases in which diagnosis was confirmed by arterial radiology; Note upon etiology of recurrent periodic ocular palsy and ophthalmoplegic migraine, Tr. Ophth. Soc. U. Kingdom 54:205, 1934.
15. Russell, W. R.: Injury to cranial nerves and the optic chiasm, in Brock, S.: Injuries of the Brain and Spinal Cord and Their Coverings, ed. 3, Baltimore, The Williams & Wilkins Company.
16. Reid, W. L., and Cone, W. V.: The mechanism of the fixed dilated pupil, resulting from ipsolateral cerebral compression, J.A.M.A. 112:2030, 1939.
17. Sunderland, S., and Bradley, K. C.: Disturbances of oculomotor function accompanying extradural hemorrhage, J. Neurol., Neurosurg. & Psychiat. 16:35, 1953.
18. Sunderland, S.: Neurovascular relations and anomalies at the base of the brain, J. Neurol., Neurosurg. & Psychiat. 11:243, 1948.
19. Sunderland, S., and Hughes, E. S. R.: The pupillo-constrictor pathway and the nerves to the ocular muscles in man, Brain 69:301, 1946.
20. Ehlers, H.: On pathogenesis of ophthalmoplegic migraine, Acta psychiat. et neurol. 3:219, 1928.
21. Wilson, S. A. K.: Neurology, London, Edward Arnold & Co., 1944, p. 1581.

Frenquel, a Blocking Agent Against Experimental LSD-25 and Mescaline Psychosis

Preliminary Note on its Clinical Application

Howard D. Fabing, M.D.

THE PRESENT STUDY of the effects of Frenquel in patients and in normal subjects stems from earlier observations on Meratran. Brown and Werner[1] found that Meratran, *a*-(2-piperidyl) benzhydrol hydrochloride, differed significantly from other central nervous system stimulants such as the amphetamines. No cardiovascular pressor reactions, no appetite loss, and little disturbance in nocturnal sleep have been observed with this compound, which may be used therapeutically in mild depressive states[2] as well as in narcolepsy and certain selected motor tic syndromes.[3] Himwich and his associates[4] state that Meratran is not a sympathomimetic drug. They have demonstrated that the central reticular substance of the rabbit brain is stimulated by the compound, followed by cortical stimulation, and Heath[5] found that Meratran has an unique ability to cause rapid high voltage activity in the septal area of the monkey electrographically.

Because Meratran appeared to be a truly central-acting compound without observable concomitant effects on the autonomic nervous system, and because its site of action appeared to be, at least in part, in the upper brainstem tegmentum, it was felt that other compounds of similar chemical configuration might also be of value as therapeutic agents in disorders of the central nervous system. A study of a group of isomers and congeners of Meratran is now in progress, and Frenquel is the first of these upon which clinical experience has been reported.[6]

Frenquel is the gamma-isomer of Meratran. It will be noted in the structural formulas that the NH radical is moved from the 2-position to the 4-position in the piperidyl ring in the synthesis of this benzhydrol compound. Brown[7] has found that this Meratran isomer of close structural similarity, a white crystalline substance, bitter in taste, and soluble 1 part in 50 of water, is far different from the parent compound neuropharmacologically. It is not a central excitant, but rather is an antagonist of central stimulation produced by other agents in the mouse, including amphetamine, morphine, cocaine, and Meratran. In a dose of 20 mg./kg. it almost doubles the sleeping time produced in mice by the intraperitoneal injection of 100 mg./kg. of hexobarbital. It is of

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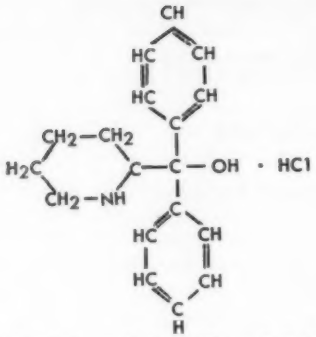
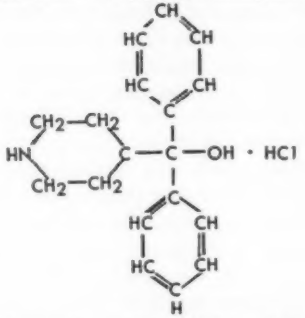


Meratran α-(2-piperidyl) benzhydrol HCl



Frenquel α-(4-piperidyl) benzhydrol HCl

extremely low toxicity in experimental animals, both in acute and chronic experiments.

EARLY CLINICAL TRIALS

Clinical trial of this compound by oral administration was begun in Christ Hospital, Cincinnati, in June 1954 and has continued until the present time. These results will be reported fully at a later date,[8] but it has now been used in approximately 75 patients. Its action is variable in the dosage range employed, but we have been impressed by the manner in which it has brought acute schizophrenic reactions to an end in an appreciable number of our small series of cases, erasing hallucinatory and delusional symptoms in a dramatic way, occasionally within a matter of hours. In a small number of cases of alcoholic hallucinosis, characterized primarily by auditory hallucinations and paranoid reactions to them, approximately one-half the patients have been relieved. Results have not been as good in senile hallucinatory states and in the more chronic schizophrenic patients, but we have been heartened by occasional excellent responses. We have found in all these groups that when electroconvulsive therapy is added to Frenquel, amelioration of symptoms seems to come about with fewer treatments than former experience would have led us to suspect in most cases. More recently, we have obtained clinical results in a few seriously involved schizophrenics which suggest that chlorpromazine and Frenquel may have a synergistic action, in that patients who do not respond therapeutically to either drug alone may improve on their simultaneous use.

Frenquel appears to have little or no effect on psychotic depressive states, nor on obsessive-compulsory disorders. Anxiety reactions *per se* are not improved by its use, as far as we have been able to determine. We have not had the opportunity to try it in acute manic excitement as yet, but since it does not benefit the depressive state, we do not look forward to any outstanding results in this type of patient. No incompatibilities with other drugs have been observed as yet, with the possible exception of sulfonamides.

Frenquel appears, then, to be an effective drug in the dissociation syndromes, but inconsistently so, as far as our observations have gone. Because of this therapeutic quality which the drug was able to exhibit on occasion, a study

of its action on "model" psychoses with hallucinogenic drugs was undertaken.

FIRST LSD-25 EXPERIMENT

In the first experiment,[9] two healthy male graduate students in psychology swallowed 100 micrograms of LSD-25 in 100 cc. distilled water[10] on the morning of November 6, 1954. Typical psychotic responses resulted. In the first subject, age 25, weighing 88 kg., a five and a half hour psychosis characterized by euphoria, vivid visual hallucinosis, marked associative looseness of thought, and dissociation from reality resulted. He wrote:

"The pervading feeling was that there was a gulf between me and the rest of the environment. It seemed that it would be impossible for me to communicate with those across this gulf because I could not establish any common points of reference. Within my own realm on my side of the abyss it was impossible to achieve any order. Attention was continually waning and there were no fixed reference points for thought to focus upon. Within this state on my side of the abyss I felt perfectly calm and entirely indifferent. Also within this state there were hallucinations and a sense of timelessness, all unusual, none of which had any real emotional tone to them."

In the second subject, aged 22, weighing 70 kg., a distressing agitated paranoid state with profound distortion of time sense, somatic hallucinations, and almost catatonic withdrawal did not come to an end for more than 13 hours. His written account reads in part:

"I had very little by way of visual hallucinations, but what *I* consider the important thing that – well, what's a word to describe it – dissociated, plagued, pounded, weighed – all these are inadequate to describe the horrible state I was in, all of them put together. Perhaps the central thing was suspicion and fear that you would find out about me, or perhaps think things that were not true. My overwhelming concern became, 'Are they doing this to find out how I'll act? Are they deliberately rattling that damned paper to make me angry?' On and on and on this went, and, as was no doubt obvious, I decided to do as little as possible so I wouldn't make any mistakes. It was my *confusion*, the fact that I had to study the situation, to be careful, that shall I say, racked me up."

On the next day both subjects were begun on Frenquel orally. The first subject was given 10 mg. twice daily in tablet form; the second was given 5 mg. in the same manner. This dose was continued throughout the subsequent week, and a final dose of 10 mg. in the first case and 5 mg. in the second case was given on arising on November 13, 1954, the date of the second LSD-25 ingestion. The only effects reported by the subjects during this week of twice daily administration of the drug were that they tended to stretch their muscles more often than usual, and that they were willing to go to bed about an hour earlier than their usual midnight retirement time. They continued with their usual academic schedule during the week of premedication. On the second Saturday, the same dose of 100 micrograms of LSD-25 in 100 cc. distilled water was given.

The first subject recorded his impressions as follows:

"The effects were markedly different on the second Saturday. The one objective feeling which stood out was that of great calm and inner peace. There was some slight defect of attention and I didn't feel sharp mentally, but I have experienced this same sort of feeling when a hard day's work has tired me out. I felt that I had the situation under control and that I was not dissociated at any time. There were no hallucinations. I felt that I could have gone through my normal routine that Saturday morning although I would have preferred that my work be of a passive sort."

The second subject wrote of his experience as follows:

"It was quite similar, yet it was so very different. Where the first time my mind began

racing and becoming tangled, eventually swallowing me up despite my efforts, the second time my efforts to fight it off were successful. In one sentence, I think it might be summed up rather adequately by saying: It was a fight both times, but the second time I won."

Frenquel, when given orally as a premedication, did not block the visceral effects of LSD-25 as it did the psychic. Slight nausea, a vague feeling of numbness in the limbs, an uncomfortable tightening of the jaws, and sweating of the extremities were noted by the first subject on both occasions. Each time the second subject developed a dry mouth, nausea, anorexia, a feeling of "jitteriness yet leadenness" in his muscles, and he noted similar though lesser sweating and conjunctival injection the second time. No significant changes in pulse, blood pressure, respiration, or pupillary size were seen on the two experimental days.

On December 18, 1954, five weeks after the second observation, the same quantity of LSD-25 was ingested by the two subjects without "protective" premedication with Frenquel to repeat the first observation. The first subject again had a five and a half hour dissociation reaction which he described as follows:

"Most of the experience was similar to the first unprotected session. The stages which I went through at the onset and at the end of the drug effect were quite similar. The same visceral and autonomic effects were noted. The same sort of visual and colored geometric illusions and intensification of colors were noted. The disruption of consecutive thought was quite evident. It was, again, as if my experience was composed of constantly changing stereopticon slides which came in an unrelated sequence. Once again it seemed that all reference points had vanished or were constantly changing so that I could not seize on any one thing and say, 'this is it.' The timeless feeling was quite evident again in this session, but as in the first session I never lost knowledge of the fact that I was in an experiment. My lack of affect was just as pronounced in this session as in the first."

INTRAVENOUS FRENQUEL DURING LSD-25 PSYCHOSIS

After ingesting 100 micrograms of LSD-25, the second subject started out with the same withdrawn, paranoid, almost catatonic reaction as before, and it appeared as though it was going to last more than 12 hours once more. In the fifth hour, however, he was given 20 mg. of Frenquel intravenously. Within a matter of minutes his expression changed, he began to lose his facial flush, and he became more animated. Rather than responding with monosyllables of *yes* and *no*, he began to speak up, to ask questions of his own, and to untangle himself from his confusion. Within 10 minutes he was asked to take another 20 mg. of the blocking agent intravenously, but his suspiciousness would not permit him to accede to the request. Within another 5 minutes he changed his mind, bared his arm, and accepted the second injection. The psychosis melted under our eyes. The sound-movie taken of this episode depicts this change in all its dramatic intensity. His own account of the episode is even more eerie to read than it was to observe:

"The first and third experiments were similar, of course. Complete and insoluble confusion and anxiety reigned, and the knowledge that its cause was a drug was my sole and small reassurance. This time I crawled onto the bed early, and planned to stay there beforehand. I was not nearly so eager to relate my experience or to cooperate with the experimenters – I was just going to wait it out this time.

"One hallucination was that of lying flat on a slowly revolving cloud-like object. There were other similar objects all around, touching gently and revolving 'in gear.' I just rolled slowly down into the depths of the arrange-

ment. Another one I recall is that of a flowerbed type of pattern, or perhaps a purposeless pin-ball machine, with the lights arranged in rows and columns. The lights – or flowers – were growing, then bursting, in irregular fashion, one at the left, then the center, and so on.

"Next occurred the phenomenon that has happened both times I 'lost,' and perhaps I have neglected to mention it previously. Things seemed to clear up and I felt sane, yet knew I wasn't. I seemed to wake up to a new world – the same situation, same people and environment, yet everything – that is, my mental state, my life – had been altered. I was a stranger in this world. I could no longer speak to anyone as a person. And that was my state when I was given the shot, bewildered, confused, afraid to say a word till I could be sure of what was happening, in which world I was.

"I realize that what happened to me in those few minutes after the injection has a tremendous significance. Because of this realization, I have worked it over often since then. But God help me, I can't tell you a thing. It just happened. There was no crescendo, no fitting together of the pieces, no breaking through the surface. All of a sudden I found myself willing to cooperate, able to follow conversation more easily, just less anxiety-ridden. I don't know how or why. I'm sorry, but that's all I can report. . . . But I was having none of the second injection, since it was a trick. Then the doctor's reassuring voice, and after I pondered awhile, agreed to take it. And again, nothing to report; I just realized I was back again in the real world, and began trying to describe my sensations."

SECOND LSD-25 EXPERIMENT

A second type of experiment has been carried out on six subjects, three female and three male. In this study a "blind" technic was employed in that the author alone knew what dosage of premedication was given, or whether placebo tablets were used, and whether LSD-25 (which is tasteless) or plain water was given on the day of the experiment. These possible variables were made clear to both the subjects and to the observers. None of the subjects reported any subjective or objective reactions during the premedication period.

The female subjects were a 30 year old hospital personnel supervisor, weighing 66 kg., a 25 year old nurse weighing 60 kg., and a 40 year old toxicologist weighing 61 kg. The first subject received 15 mg. of the blocking agent daily for a week of premedication; the second, 20 mg.; and the third, 30 mg. in divided doses. Since tablets of varying strength and similar appearance were available, it was possible to keep the patients in complete doubt about the quantity of blocking agent they were receiving, and since they had no distinctive taste the subjects were not sure whether they had been given placebos or medication. On the experimental day, all were given 100 micrograms of LSD-25 in distilled water, but were not informed of the contents of the drink.

The first patient, the personnel supervisor, read magazines through the morning, was somewhat nauseated, and "knew that she had something" because of a numb feeling in the right arm and hand. Throughout the experimental period she occupied herself with her usual problems of the 800 employees she has in her charge, and stated that she could have spent the time occupied by the experiment at her desk, although she would have had trouble typing because of the numbness of her right hand. The nurse, a cheerful person by nature, "got the giggles," and she developed some spatial disorientation, reporting that people and objects looked closer or more distant at times, as did her own hands, but she did not develop any symptoms of dissociation of thought or dreamy drift from reality. On one occasion, she reported seeing wavy colored lines on the ceiling during the second hour but this was

fleeting. The third subject, the toxicologist, experienced waves of nausea which were quite uncomfortable and some attention defect with a lowering of her mood level when the nausea was severe, but she reported no association defects in the continuity of her thought processes, no hallucinations, and no autistic drift from the reality situation.

The three males were a hospital orderly, an Appalachian Mountain boy of limited educational attainments, aged 19, weighing 61 kg.; a senior medical student, aged 28, weighing 74 kg.; and an intern, aged 27, weighing 80 kg. Without knowledge of what they were given as premedication, they received 30, 10, and 10 mg., respectively, of the gamma-isomer of Meratran daily in divided doses for a week prior to the experiment. They were given a drink, the nature of which they did not know, but which in each case consisted of 100 micrograms of LSD-25 in 100 cc. distilled water.

The orderly had been teased by his fellow workers all during the week prior to the experimental day, and he arrived on the scene apprehensive and fearful. As the morning wore on and he experienced nothing beyond minimal nausea and slight languor, his apprehension abated and he grew progressively more composed. The medical student had a troublesome attention defect which bothered him because he wanted to keep alert to everything which was going on in the experimental situation, and he had difficulty in doing so. He is an athletic sort of person, and stated at the height of his attention defect in the third hour, "If I could get out and kick a football around a bit, I'd work off this dull feeling in my head." It ended abruptly in the fourth hour. At no time did he hallucinate nor did he lose his reality orientation.

EFFECT OF INCREASING FRENQUEL DOSAGE

The intern, a sensitive person of high intellectual attainments for his age, and a quiet, inhibited sort, became loquacious and thrilled by the rush of his thoughts. He wrote a long account of his psychic reaction which cannot be recorded fully here. In part he said:

"The largest component was that of pure emotional response and as unaccountably moving then as now . . . . It occurred as if by a spontaneous evolution out of all the moments of exquisite and aching joy that one has ever known, and there arose a profound sense of awe, of adoration of nothing specific, and of almost worshipful gratitude to the unknown cause of such pure and unblemished happiness."

Visual hallucinations of amorphous swirls of color, and again of green forests, and "an almost unspoken voice arising in response to the overwhelming abundance of sensation" occurred as well.

Because he developed this state of rapture, depersonalization, and hallucinosis despite the daily administration of 10 mg. of the blocking agent for a week prior to swallowing 100 micrograms of LSD-25, he was asked to continue the same number of tablets and to return the following Saturday. On this occasion, he was given five 5 mg. tablets of Frenquel twice daily, instead of five 1 mg. tablets of similar appearance, and was not told of the change. LSD-25 was given in the same 100 microgram dose after this week of premedication with 50 mg. daily of the blocking agent. On the second occasion, he read a book and had nothing of the poetic flight of thinking, characterized by tenuous and partial associativeness, nor of the hallucinatory experiences of the pre-

vious week. He stated that he could have carried out his intern's duties with his usual level of efficiency. The sense of fascicular twitching in his somatic musculature, a dry mouth, and a sensation of tightness in his perineal region with a consequent feeling that he would soon defecate occurred on both occasions.

EXPERIENCE ON SHORTENED FRENQUEL PREMEDICATION PERIOD

In order to test whether a full week of premedication with Frenquel is necessary to produce blocking of LSD-25 psychosis, two patients were given four doses of 50 mg. of this medication at 50, 38, 26, and two hours before the ingestion of 100 micrograms of the hallucinogen. The first, a freshman medical student, weighing 85 kg., had uncontrollable giggling for most of the third hour of the experiment and complained of some attention defect, but he was otherwise unaffected in the psychic sphere. His euphoric state proved unpleasant to him, and he declined further experimentation. The second, a machinist, aged 28 and weighing only 55 kg., had complete blocking of psychotic reactions, but was disturbed by waves of nausea, dry mouth, a tight sensation in the calf and thigh muscles, and a flushing of the skin which made him feel feverish. A short period of tachycardia occurred in the third hour in this case, and he complained of tunnel vision on occasion during the experiment.

Although further observations will be necessary to determine the minimal time-against-dose relationship in the blocking of LSD-25 psychosis with Frenquel, these results indicate that a full week of premedication is not needed. The interval between the last Frenquel tablet and LSD-25 ingestion has been no longer than two hours in any of these trials, and it is uncertain how long this period might be extended, but clinical experience with two schizophrenic patients who abandoned Frenquel treatment suggests that it may prove to be a week or more.

EXPERIMENT ON MESCALINE PSYCHOSIS

On December 31, 1954, we made our first trial of Frenquel as a blocking agent against mescaline psychosis.[11] The first subject was the machinist used in the previous LSD-25 experiment. He was given four doses of 50 mg. each of Frenquel, again at 50, 38, 26, and two hours prior to swallowing 0.4 gm. mescaline sulfate. He developed more nausea than he did on LSD-25, and the subjective feeling of tension in his leg muscles and his low back was extreme, lasting almost 10 hours. There were no psychic accompaniments, however, beyond an occasional flicker of black shadows in the extreme periphery of his visual fields bilaterally.

A similar experiment was carried out on another hospital orderly, aged 20, weighing 64 kg. He became nauseated at the end of the first hour and vomited. During the fourth hour, while lying down, he stated that he got "scrambled up in my thinking" for about 10 minutes, but this cleared up as soon as he entered into conversation with observers once more. There were no hallucinations, but he seemed to experience a disruption of the continuity of thought during this short period.

A third subject, a big, burly 45 year old orderly, weighing 90 kg., was given 0.4 gm. mescaline sulfate after two days of premedication with placebo tablets which looked like those of Frenquel, and he was not told the difference. He de-

veloped a drunken euphoria "like about six quick double Martinis." He is ordinarily a conscientious and reliable person with a high sense of duty, but during this period his reaction was, "to hell with the job – let the other suckers around here do the sweating – I feel fine, and I'd like to stay like this." He experienced sensations of levitation, in which the walls, floor, and ceiling seemed to sway constantly, and his body could not find its equilibrium in this moving world subjectively, although his gait was undisturbed. He reported no true hallucinations, but said that red-colored objects seemed fluorescent during the third hour. No dissociation of thought occurred. At the four and a half hour mark, he was given 100 mg. Frenquel intravenously. Within minutes his euphoria abated, and within 15 minutes the levitation sensations stopped. Quickly he developed his normal concern about getting back to work, and by the fifth hour he resumed his regular hospital duties. He described the dramatic effect of intravenous Frenquel as being "knocked down off cloud No. 13."

The fourth subject, a 30 year old male physiotherapist, weighing 73 kg., was pretreated with placebos, as was the previous patient, prior to the ingestion of a 0.4 gm. capsule of mescaline sulfate. Somatic hallucinations of clamminess, numbness, and coldness seemed to ascend from his feet to his jaws, and then the sensation of coldness became extreme. He complained, "If I could only shiver, I'd get over this wretched coldness." He described the coldness as that which occurs to a spectator at a Thanksgiving Day football game when he becomes numb with cold. Pins stuck through a fold of his skin provoked no pain "because I am numb with cold." He stated that he felt like two persons, that he could not make any sense out of reading matter placed before him because "my mind can't work because I am too cold." At the fourth hour he suddenly became nauseated and vomited abruptly. At the fifth hour 100 mg. Frenquel was given intravenously. Within seven minutes he reported that he was warm again, and soon thereafter stated that his confusion of thought had abated. Thirty minutes later he started on a shopping tour with his wife, but still felt somewhat nauseated.

WORK IN PROGRESS

As yet little is known to us of the neurochemistry of the blocking reaction of Frenquel, either in clinical disorders or in model psychoses. We are impressed with the fact that hallucinogenic substances which have known chemical structures contain an indole nucleus, as has been pointed out by various authors,[12] and we are pursuing this line of inquiry, among others, in the hope of gaining a more dynamic interpretation of our clinical findings. An understanding of the neurochemistry of these reactions appears to be the key to future progress in this field. We plan to study the blocking effect of Frenquel on other hallucinogens, such as cannabis, harmine, and adrenochrome, as these substances become available to us.

Preliminary observations indicate that Frenquel may be of therapeutic benefit in acute postoperative psychotic states. Moreover, one patient with delirium tremens experienced cessation of his hallucinations of multicolored bugs crawling on the ceiling within 15 minutes after intravenous injection of 100 mg. of Frenquel. It is hoped that further trials will confirm this startling result.

PROPOSAL FOR NEW TERM

It appears that the advent of chlorpromazine, the rauwolfia fractions, and new Frenquel presage a new era in neuropharmacology. It requires little effort of the imagination to guess that other compounds having similar pharmacologic action will be forthcoming, now that the door seems to have been opened. What shall they be called? The term most commonly used up to this time, "tranquilizing agents," is not adequate.

A classicist[13] has suggested a word of Greek derivation. The Epicureans were especially fond of the word *"ataraxia"* which meant *freedom from confusion, peace of mind* to them. The adjective was *"ataraktos"* meaning *without confusion, steady, cool-headed.* The noun was taken over into the Latin in its entirety as *ataraxia,* and the English form, *ataraxy,* is defined in the Revised Shorter Oxford Dictionary as "freedom from disturbance of mind or passion."

Our glossary is an already overburdened one, and any proposal to enlarge it should be approached with caution. There are occasions, however, when new experience calls for a word to encompass it. Such seems to be the case with these fascinating new drugs which act upon the nervous system. It is proposed, therefore, that drugs of this type be designated *ataraxics,* and that the adjectival form, *ataractic,* be used to describe this therapeutic property in drugs. Perhaps such a name will help to tie our thinking together, and will assist us along this new road of inquiry.

CONCLUSIONS

1. Compounds with a chemical configuration similar to that of Meratran have been studied in the hope that they might be used as therapeutic agents in central nervous system disease.

2. The gamma-isomer of Meratran, *a*-(4-piperidyl) benzhydrol hydrochloride, (Frenquel) has demonstrated interesting, though inconsistent, therapeutic properties in some scihzophrenic dissociation syndromes in the dosage range used.

3. Because these clinical effects were obtained, this compound has been used as a premedication to block model LSD-25 and mescaline psychoses.

4. Two subjects, who developed typical psychoses after ingesting 100 micrograms of LSD-25, failed to develop them a week later after premedication with this blocking agent during the intervening week. During a third unprotected test five weeks later, the LSD-25 psychosis was brought to an abrupt end in one of the subjects by the intravenous injection of Frenquel.

5. Five subjects in a blind experiment developed no LSD-25 psychosis, or only fragments thereof, on doses of the blocking agent varying from 10 to 30 mg. daily for one prior week.

6. A sixth subject, who developed a schizophrenic dissociation state despite 10 mg. daily of the blocking agent for a week prior to LSD-25 ingestion, was fully blocked on a second occasion after his dose was raised to 50 mg. daily during the premedication week.

7. The compound does not appear to block the viscerosympathetic components of the LSD-25 reaction.

8. Two observations suggest that the premedication period with Frenquel may be reduced to two days. The duration of Frenquel's blocking ability has not been determined, but may prove to be a week or more.

9. Four observations suggest that model psychoses produced by mescaline

sulfate can be controlled by Frenquel in the same fashion as those induced by LSD-25 ingestion.

10. Trials of Frenquel in other acute psychotic disorders have been instituted, and trials of this blocking agent against other hallucinogenic drugs are planned.

11. Attempts are being made to understand the chemodynamics and pharmacodynamics of Frenquel.

12. A proposal is made to adopt the generic term, *ataraxics*, for pharmacologic agents such as chlorpromazine, rauwolfia compounds, Frenquel, and others, which bring about *ataraxy*, or freedom from confusion.

Both the Frenquel and Meratran used in this study were supplied by the department of medical research of The Wm. S. Merrell Company, Cincinnati, Ohio.

The LSD-25 employed in these experiments was supplied by the Sandoz Chemical Works, Inc., New York City.

The mescaline sulfate employed in these experiments was obtained from S. B. Penick and Company, New York City.

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REFERENCES

1. Brown, B. B., and Werner, H. W.: J. Pharmacol. & Exper. Therap. 110:180, 1954.
2. Fabing, H. D., Hawkins, J. R., and Moulton, J. A. L.: Am. J. Psychiat. In press; Pomeranze, J.: J. Gerontol. 9:486, 1954; Antos, R.: Arizona Med. 11:397, 1954; Levy, S.: Northwest Med. 53:1233, 1954.
3. Fabing, H. D.: Tr. Am. Neurol. A. 79:139, 1954. Fabing, H. D.: Dis. Nerv. System 16:15, 1955.
4. Schut, J. W., and Himwich, H. E.: Am. J. Psychiat. In press.
5. Heath, R. G.: Discussion of Fabing, Tr. Am. Neurol. A. 79:162, 1954. Monroe, R. R., Heath, R. G., Mickle, W. A., and Miller, W.: In press.
6. Fabing, H. D.: Science 121:208, 1955.
7. Brown, B. B.: Unpublished data.
8. Fabing, H. D., and Hawkins, J. R.: Unpublished data.
9. Fabing, H. D.: A 16-mm. sound-movie in color, "Experimental Compound MER-17, A New Blocking Agent Against LSD-25 Psychosis," shown at A.P.A. Regional Research Meeting, Galveston, Texas, February 19, 1955.
10. Stoll, W. A.: Schweiz. Arch. Neurol. u. Psychiat. 60:279, 1947; Schweiz. med. Wchnschr. 79:110, 1949.
11. Beringer, K.: Der Meskalinrausch, Monograph, aus dem Gesemtgebrete der Neurologie und Psychiatrie, Berlin, 1927; Kluver, H.: The Divine Plant, Kegan, Paul, Trench, Trubner and Co., Ltd., London, 1928; Stockings, G. T.: J. Ment. Sc. 86:29, 1940; Huxley, Aldous: The Doors of Perception, Harper and Bros., New York, 1954.
12. Hoffer, A., Osmond, H., and Smythies, J.: J. Ment. Sc. 100:29, 1954; Woolley, D. W., and Shaw, E.: Brit. M. J. 126:122, 1954; Gaddum, J. H.: Ciba Symposium on Hypertension, p. 75, London, 1953; Erspamer, V.: Pharmacol. Rev. 6:425, 1954. Nieuwenhuyzen, F. J.: Proc. Acad. Sci. Amsterdam 39:1151, 1936; Evarts, E.: Symposium on Medicinal Chemistry, Univ. Syracuse, June 16-19, 1954.
13. Cameron, Alister: Professor of Classics, University of Cincinnati.

Temporal Lobe Seizures in the Monkey

Jorge Huertas, M.D. and Francis M. Forster, M.D.

In 1953 a region of the temporal lobe of the Macaca mulatta was described which contained some points from which suppression of electrical activity could be obtained.[1] These did not comprise one sharp area, but consisted of a series of points gathered in the first temporal convolution inferior to the base of the rolandic fissure. At that time the possible significance of these points in convulsive disorders was suggested, and it was with that concept in mind that the original investigations were begun. The possibility of a suppressor mechanism playing a role in seizures, and particularly in psychomotor seizures, was suggested by Penfield's[2] statement that these latter attacks should instead be called psychoparetic seizures in view of the suspension of corticomotor activity during their course.

This paper presents further data from experiments on the suppressor region of the temporal lobe, and presents the effects of stimulation of these areas of the monkey in the waking state.

MATERIAL AND METHODS

These experiments were carried out on a series of 11 Macaca mulatta. In all animals the suppressor points of the temporal lobe were carefully delimited, as described previously.[1] Alumina disks, using the method of Kopeloff,[3] were placed over the suppressor region in three of these monkeys, lead electrodes were embedded in three, and silver wire electrodes were placed on the cortex in four.[4] The lead electrodes were intended as secondary coils to be activated by a primary coil built into the animal's cage. All procedures were done under sterile, aseptic technic. After identifying the suppressor region, care was taken to tag it with soft paper and to place the permanent electrodes and alumina disks on these tagged areas.

RESULTS

Suppressor seizures were elicited in the monkeys with the silver wire embedded electrodes when these electrodes were activated. Best results were obtained by using a 50 cycle, 4-volt current. When the animal was restrained so that his brain waves could be obtained before, during, and after stimulation, this period of suppressor seizure coincided with a period of decrease in electrical activity.

In the restrained animal, the suppressor seizure consisted of loss of the usual defensive reflexes and an obvious impairment of the animal's usual alertness.

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Ordinarily placing objects in the monkey's mouth immediately causes him to bite, and when frightened he will rear away. In the course of these suppressor seizures the animal lies listless and the examiner's finger can be inserted into the mouth without eliciting a response. In one instance a fly was walking across the animal's mouth and no response was obtained.

When the suppressor regions are stimulated in unrestrained animals, they lean far forward, drop to their haunches, hang their heads dejectedly, and do not respond to auditory, visual, or tactile stimuli. This period of decreased activity and awareness occurs usually two to three minutes after the stimulation and may last from one to three minutes. It is usually over quite abruptly, so that the animal very quickly and suddenly leaps into full activity and occasionally may begin to chew and bite wildly at objects. There is sometimes a rebound second episode of decreased electrical activity and decreased activity in the animal; this usually occurs after a period of five to ten minutes and is not as pronounced as the first episode.

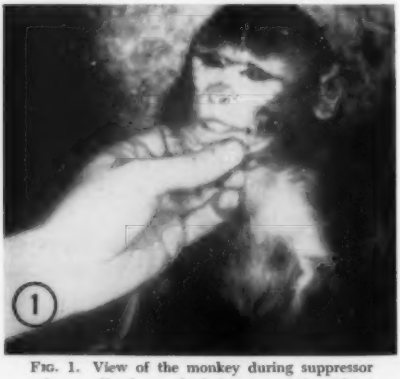

FIG. 1. View of the monkey during suppressor seizure. Food pouch being emptied without resistance.

The application of alumina cream disks failed to produce any seizure manifestations in the animals. Those to which they were applied are still alive and the observation of them is continuing (two years).

An interesting observation, however, was that the lead-coil embedded electrodes produced spontaneous seizures. When not in seizures and when viewed in the open cage, these animals showed all the usual defensive reactions of the species, flying to the corner of the cage, showing natural startle reactions, and clambering up the cage to avoid capture. However, during the spontaneous attacks they become quite limp, and do not respond when the examiner reaches out for them (figure 1). Feeding is impossible, and the animal may be lifted, one hand after the other, from the side of the cage. Placed in the middle of the cage he sinks listlessly to the floor, his eyes do not follow objects, his head hangs down to some extent, and again the finger can be inserted into the mouth and the food pouches emptied without any danger to the examiner. These episodes also last one to three minutes, but peculiarly occur in series over a period of an hour or more, separated by a free interval of a few minutes. The monkeys have three or four series of such attacks a month. The electroencephalogram shows characteristic changes during such attacks. Usually there is random spiking activity from the lead over the involved temporal lobe. Suddenly this spiking activity increases and the other leads begin to show suppression of their electrical activity. In two to four minutes there is marked suppression, and it is during this period that the above described seizures are noticed (figure 2).

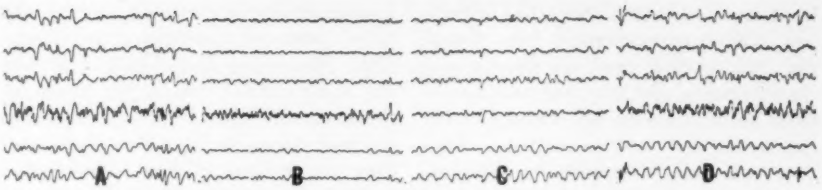

FIG. 2. Electroencephalogram before, during, and after temporal suppressor seizure, induced in the monkey by lead electrodes. The first two lines of the tracing correspond to the frontal leads, lines three and four correspond to the temporal leads, and lines five and six correspond to the parietal leads. A. Monkey awake, activity normal except electrical discharge right temporal. B. 80 seconds later: Monkey unresponsive, suppression of electrical activity. Slight discharge in right temporals. C. 20 seconds later: Monkey unresponsive. Suppression. D. 40 seconds later: Monkey awake, activity returned.

DISCUSSION AND CONCLUSIONS

Psychic manifestations of epilepsy of the temporal lobe were first described by Hughlings Jackson[5] as a "peculiar variety of epilepsy characterized by exceedingly complex and very purposeful seeming actions during continuing unconsciousness." These seizures, he deduced, arose from lesions of the temporal lobe. In recent years electroencephalography has added considerably to the entire understanding of temporal lobe seizures, especially the work of Gibbs and Gibbs[6] who demonstrated the validity of sleep records in patients with temporal lobe lesions particularly in patients with psychomotor seizures. Penfield[7] recently described the psychic mainfestations elicited by electrical stimulation of the temporal lobe, and Merlis and Golub[8] pointed out the phases of psychomotor seizures and described an initial phase of arrested psychic and motor activity. Jasper,[9] discussing depression of the electroencephalogram preceding the onset of an epileptic discharge, suggested that "this seems to be a special process in only certain brain areas which perhaps have a type of 'suppressor' or inhibitory function."

The demonstration of the suppressor region of the temporal lobe may lead to a further elucidation of the manifestations of psychomotor epilepsy, and for that reason the present studies were continued. The peculiar seizures observed resulting from stimulation of suppressor regions and associated with the decrease in electrical activity of the cortex are, it is believed, a type of temporal lobe seizure. It is possible that one could not expect much more in the way of temporal lobe seizures in the macaque. After all, in patients with psychomotor epilepsy, the clinical pattern of the seizures depends upon their life experience. One patient previously described had a psychomotor seizure during the playing of the Star Spangled Banner; he remained seated in his chair and demonstrated anger by cursing.[10] It is not possible for the monkey to show, by cursing and movements such as restless stroking of the arms of the chair, the same kind of experience pattern. Even more dramatic, of course, are the patients who suddenly break into the repetition of a poem or a prayer or the singing of a song. These, of course, are patterns of experience of the patient, and beyond the ken of the monkey. It was noteworthy, however, that at no time did any of the animals vocalize during their seizures.

The failure of the alumina cream disks

to produce seizures is somewhat disturbing. Other experimenters have found that this method does not always produce seizures, and that the best results from alumina cream are obtained over the motor and sensory cortices. However, this was not feasible for the present experiments since application had to be made to the temporal lobe. The alumina cream disks used in the present study thus far have failed to induce seizures although they have been in place for periods of 12 months to two years.

The appearance of seizures in the monkeys with lead electrodes in place over their suppressor regions merits special comment. These lead electrodes were intended as secondary coils and a primary coil was planned on the outside of the cage. However, before the cage could be constructed, these monkeys began to have spontaneous seizures. It is not yet known why these particular coils should have produced convulsive manifestations. Histologic and chemical studies are being carried out on the brains of these animals and chemical analyses of the lead electrodes have been instituted. The total problem of these epileptogenic foci is being studied. The importance of a simple technic such as this for producing experimental epilepsy is obvious.

SUMMARY

1. Electrical stimulation of the suppressor region of the temporal lobe in Macaca mulatta produces transient periods of decreased activity and apparent loss of consciousness. These can be called suppressor seizures.

2. The implantation of lead coil electrodes over the same suppressor regions produces a chronic epileptic state characterized by suppressor seizures.

REFERENCES

1. Huertas, J., O'Doherty, D. S., and Forster, F. M.: Evidence of suppression from the temporal lobe in the monkey, Arch. Neurol. & Psychiat. 70: 393, 1953.
2. Penfield, W.: Epileptic manifestations of cortical and supracortical discharge, E.E.G. & Clin. Neurophysiol. 1:3, 1949.
3. Kopeloff, N., Whittier, J. R., Pacella, B. L., and Kopeloff, L. M.: The epileptogenic effect of subcortical alumina cream in the Rhesus monkey, E.E.G. & Clin. Neurophysiol. 2:163, 1950.
4. Huertas, J.: A simple method for stimulation of the cerebrum, Bull. Georgetown Univ. M. Center 6:175, 1953.
5. Jackson, J. H.: Selected Writings of John Hughlings Jackson. Vol. 1. London, Hodder and Stoughton, 1931.
6. Gibbs, F. A., and Gibbs, E. C.: Psychomotor epilepsy, Arch. Neurol. & Psychiat. 60:331, 1948.
7. Penfield, W.: Epileptic Seizure Patterns. Springfield, Ill., Charles C Thomas, 1951.
8. Golub, L. M., Guhleman, H. V., and Merlis, J. K.: Seizure patterns in psychomotor epilepsy, Dis. Nerv. System 12:73, 1951.
9. Jasper, H. H.: Electrical signs of epileptic discharge, E.E.G. & Clin. Neurophysiol. 1:11, 1949.
10. Forster, F. M.: Psychomotor epilepsy, J.A.M.A. 145:20, 1951.

Reflections on the Pathogenesis of Progressive Muscular Dystrophy

Ib Persson

PROGRESSIVE MUSCULAR DYSTROPHY is a disease on whose pathogenesis there has been no agreement, but the results of research of recent years in this field are such that it seems reasonable to set forth the following new theory of its pathogenesis. The essential experimental findings on which the new theory is built concern metabolism in normal muscle and in progressive muscular dystrophy. In progressive muscular dystrophy it has been demonstrated that there is a reduction in the amount of myoglobin[1] and myosin.[2] Analysis has shown that there is a reduction of the nonheminbound iron when this is estimated in fat free muscles.[2] Indovina[3] found a low serum iron in patients who manifested very advanced muscle dystrophy. When cytochrome C was given to patients who had progressive muscular dystrophy, a considerable diminution in the amount of creatine in the urine could be seen.[4] Beinert[5] has shown, by means of isotope experiments with iron, that 24 hours after the injection there was none of the injected cytochrome C intact in the body, and the iron was distributed in the various organs. In investigating a patient with progressive muscular dystrophy, Milhorat[4] found that he could bring about the same diminution of creatine in the urine in giving an iron salt instead of cytochrome C.

Part of the iron in muscle occurs in an as yet incompletely understood combination with the actomyosin, and this combination can initiate a contraction on addition of adenosine triphosphate.[6] When energy is used up in muscle, the adenosine triphosphate is broken down into adenosine monophosphate[7] and is built up again with energy, some of which is generated at the breakdown of creatine phosphate. This last process causes the excretion of creatinine in the urine.[8]

Certain investigations in connection with progressive muscular dystrophy have shown that there is a reduction of adenosine triphosphate per gram of muscle.[9] Others[10] have found that even if there is a reduction of the absolute quantity of adenosine triphosphate, at the same time there is a relative increase when the investigations are based on the quantity of fully acid-soluble phosphorus. But this only seems to indicate that the creatine and phosphocreatine disappear more quickly than the adenosine

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triphosphate. Presumably the essential point is that the total content of the adenosine triphosphate in the muscles is reduced, and that the active muscle mass is replaced by fat and connective tissue.

It is to be expected, consequently, that the muscles use less creatine than normally, as less is required for the synthesis of a lesser quantity of adenosine triphosphate in the muscles. Thus Nevin[11] has shown that the breaking down of creatine phosphate is less than normal. It has also been learned through isotope experiments[12] that there is a reduced consumption of creatine in striped muscle in this disease, and that there is an imbalance between the almost normal rate of production of creatine and the active muscle mass, which shows in the occurrence of creatinuria.

In progressive muscular dystrophy, creatinuria is the chemical abnormality which has been given special attention. However, this sign is not necessarily pathognomonic of this disease, as it may be absent, especially in the early stages.[4] Moreover, creatinuria is found in other diseases of muscle and in spinal muscle atrophies. Even if creatinuria is not, therefore, specific for progressive muscular dystrophy, the frequent appearance of this sign and the frequently highly raised values have come to be regarded as important in the diagnosis and research into the pathogenesis of the disease.[13–16] In the form of muscular dystrophy which can be produced in certain species of animals through enforced vitamin E deficiency and which in essential features resembles progressive muscular dystrophy in man, one could both cure and straightaway lessen the creatinuria through the administration of alpha-tocopherol.[17]

This effect of vitamin E becomes of special importance for the theory now proposed, in that it has been shown that this vitamin has a regulating effect on adenosinetriphosphatase.[18] On the other hand, alpha-tocopherol has no effect on progressive muscular dystrophy in man, nor does it diminish creatinuria,[15,19] even if clinically and morphologically this disease otherwise much resembles that form of muscular dystrophy which is seen in animals having enforced vitamin E deficiency.

The above mentioned findings suggest that the pathogenesis of progressive muscular dystrophy is an abnormality in the combination between the iron-actomyosin and the adenosine triphosphate, which initiates contraction of muscle. This causes a decrease in the amount of adenosine triphosphate in muscle. The condition can either be caused by inherited or acquired factors.

Thus, the creatinuria in progressive muscular dystrophy can be explained through the fact that, owing to the reduced amount of adenosine triphosphate, the consumption of creatine is reduced. The creatinuria in spinal muscle atrophies may be attributed to the lack of function of the muscles in these diseases, as the consumption of energy and consequently the consumption of creatine as a source of energy are reduced. Correspondingly it has also been shown that there is lessened activity of adenosinetriphosphatase in denervated muscles.[20] This results in an excess of creatine which is excreted.

The theory here advanced may also serve to explain why vitamin E has no effect on progressive muscular dystrophy in man, even if otherwise this disease clinically and morphologically bears a strong resemblance to the muscular dystrophy which can be produced in cer-

tain animal species by means of enforced vitamin E deficiency. In spite of their great similarity, however, the fundamental difference between the two diseases is thought to be that progressive muscular dystrophy is presumably due to a reduced content of adenosine triphosphate in muscle, while the dystrophy in animals is supposedly due to a disturbance in the functions of the adenosinetriphosphatase. Similarly, Kalckar[10] has not found any change in the adenosine triphosphate content in the affected muscles in animals suffering from vitamin E deficiency.

SUMMARY

On the basis of investigations concerning metabolism in normal muscle as well as that in progressive muscular dystrophy, the theory is propounded that the pathogenesis in progressive muscular dystrophy is an inherited or acquired disturbance in the combination between the iron-actomyosin and the adenosine triphosphate, which causes contraction of muscle. This gives rise to a diminution in quantity of the adenosine triphosphate in muscle, with consequent creatinuria.

REFERENCES

1. Meldolesi, G.: Le miopatie primitive con particolare riguardo alle distrofia muscolare progressivea, Rome, Pozzi, 1938.
2. Dreyfus J., and Schapiro, G.: Le Muscle. Etude de biologie et de pathologie, France, L'Expansion Scientifique, 1952.
3. Indovina, I.: Sul ricambio del ferro nei miopatici primitivi, Boll. Soc. ital. biol. sper. 23:4, 1947.
4. Milhorat, A.: Le Musle. Etude de biologie et de pathologie, France, L'Expansion Scientifique, 1952.
5. Beinert, H.: Studies on the metabolism of administered cytochrome C by the aid of iron-labeled cytochrome, Science 111:469, 1950.
6. Szent-Gyorgyi, A.: Chemistry of Muscular Contraction, New York, Academic Press, 1947.
7. Varga, L.: The relation of temperature and muscular contraction,, Acta Phys. Hung. 1:1, 1946.
8. Borsook, H., and Dubuoff, J.: The hydrolysis of phosphocreatine and the origin of urinary creatinine, J. Biol. Chem. 168:493, 1947.
9. Reinhold, J., and Kingsley, G.: The chemical composition of voluntary muscle in muscle disease. J. Clin. Investigation 17:377, 1938.
10. Kalckar, H. M.: Le Muscle. Etude de biologie et de pathologie, France, L'Expansion Scientifique, 1952.
11. Nevin, S.: A study of the muscle chemistry in myasthenia gravis, pseudohypertrophic muscular dystrophy and myotonia, Brain 57:239, 1934.
12. Roche, M., Benedict, J., Yii, T., Bien, E., and Stetten, D.: Origin of urinary creatine in progressive muscular dystrophy, Metabolism 1:13, 1952.
13. Harris, M.: Negative therapeutic and metabolism effects of synthetic alpha-tocopherol in muscular dystrophy, Am. J. M. Sc. 202:258, 1941.
14. Milhorat, A., Toscani, V., and Bartels, W.: Effect of wheat germ on creatinuria in dermatomyositis and progressive muscular dystrophy, Proc. Soc. Exper. Biol. & Med. 58:40, 1945.
15. John, S.: Erfahrungen über die Behandlung der progressiven Muskeldystrophie mit Inosit und Vitamin E, Ztschr. Med. klin. 148:245, 1951.
16. Bleiching, E. P.: Ueber Stoffwechsel-Untersuchungen bei progressiver Muskeldystrophie und die Ergebnisse einer Behandlung mit Vitamin E., Mainz, 1953.
17. Evans, H., and Burr, G.: Development of paralysis in the suckling young of mothers deprived of vitamin E, J. Biol. Chem. 76:273, 1928.
18. Feuer, G., and Frigyes, A.: Change of adenosinetriphosphatase activity in the case of muscular dystrophy due to vitamin E deficiency, Acta Phys. Hung. 3:1, 1952.
19. Bang, J., Einarson, L., Fog, M., and Ringsted, A.: About the treatment of neuro-muscular diseases with synthetic vitamin E. Nord. med. 10:1201, 1941.
20. Zubenko, P., Reba, A., and Plachotisina, E.: Biochimija 15:79, 1950.

Clinical and Laboratory Findings in Two Hundred Head Injuries

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TWO HUNDRED HEAD INJURIES representing almost all types of trauma to the head were selected at random from World War II casualties at Cushing General Hospital from June 1944 to January 1946. These 200 cases were subdivided into open head injuries without penetration of the dura, open head injuries with penetration of the dura, and closed head injuries, that is, cerebral concussion or contusion of the brain without gross injury to the skull or penetration of the dura. It was also noted as nearly as possible which lobe or lobes of the brain were injured (table 1).

Injury to the brain in this study was due to shell or shrapnel fragments in over half of the patients. Direct bullet or gunshot wounds of the brain were the second most common cause of intracranial injuries (table 2).

As accurate a history as possible was obtained from each patient and the information was checked carefully with the overseas medical records or records of transfer from other hospitals. Soon after admission to the head injury service, each patient had a thorough neurologic examination, roentgenogram of the skull, electroencephalogram, spinal puncture, routine urine and blood studies, and psychologic tests. After these studies were completed, the patient was seen in conference with the neurosurgeon to determine if any surgical procedures should be carried out. A little over half of the open head injuries required insertion of tantalum plates to repair skull defects. At the time of the brain operations, the appearance of the dura or brain was carefully noted in the operative record. The question of removal of retained foreign bodies within the brain was weighed carefully by both the neurologist and the neurosurgeon. The problem of resection of an epileptogenic focus was considered only after more accurate electroencephalograms under activation were done.

The majority of patients with open or penetrating wounds of the skull or brain had at least two electroencephalograms. Insertion of a tantalum plate over the area of brain damage had no effect on subsequent recordings. Patients with

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TABLE 1
CLASSIFICATION OF HEAD INJURIES ACCORDING TO TYPE AND LOCATION

Location	*Open Non-Penetrating*	*Open Penetrating*	*Closed*	*Total*
UNILOBAR				
Right frontal	5	11	1	17
Left frontal	2	11	1	14
Right temporal	0	6	0	6
Left temporal	4	6	1	11
Right parietal	4	19	7	30
Left parietal	1	17	8	26
Right occipital	0	2	3	5
Left occipital	0	8	3	11
TOTAL	16	80	24	120
BILATERAL				
Frontal	0	5	0	5
Temporal	0	0	0	0
Parietal	0	3	0	3
Occipital	0	4	6	10
TOTAL	0	12	6	18
MULTIPLE LOBAR				
Right frontotemporal	0	0	0	0
Left frontotemporal	1	0	0	1
Right frontoparietal	0	4	0	4
Left frontoparietal	1	4	0	5
Right temporoparietal	0	3	3	6
Left temporoparietal	0	2	3	5
Right parietooccipital	1	3	0	4
Left parietooccipital	1	6	0	7
Right frontoparietooccipital	0	2	0	2
Left frontoparietooccipital	0	0	0	0
TOTAL	4	24	6	34
Cerebral concussion group (non-focal)	0	0	28	28
TOTAL	20	116	64	200

TABLE 2
MODE OF INJURY TO THE HEAD

	Head Injury			
	OPEN		CLOSED	
	Non-penetrating	*Penetrating*		*Total*
Shell or shrapnel fragment	11	90	9	110
Bullet wound	4	22	4	30
Shell or mine explosion	0	0	18	18
Auto or plane accident	3	2	17	22
Falling object	2	1	6	9
Fall of the patient	0	1	10	11
TOTAL	20	116	64	200

normal electroencephalograms were not repeated, but all borderline records were rechecked. Many patients were on small doses of phenobarbital, but this did not seem to change the records and was not withheld before the electroencephalograms were made.

The clinical factors studied in relationship to the cerebral trauma included the duration of unconsciousness, neurologic signs, electroencephalographic findings, mental changes, epileptiform seizures, aphasia, degree of brain damage, headaches and dizziness, and disposition. The degree of impairment under each of these clinical factors was graded as 0 – no change; 1 – slight change; 2 – moderate change; and 3 – severe change (table 3).

PART 1 – CLINICAL AND LABORATORY FINDINGS ACCORDING TO REGION OF THE BRAIN INJURED

For the sake of brevity and to avoid burdening the reader with a great deal of statistical figures, only the results of the greatest degree of clinical and lab-

TABLE 3
CLINICAL FACTORS AND THE DEGREE OF IMPAIRMENT

	0	*1*	*2*	*3*
1. Duration of unconsciousness	None	Less than 1 hour	1 to 24 hours	Over 24 hours
2. Neurologic signs	None	Mild	Moderate	Severe
3. Electroencephalographic findings	Normal	Slow wave focus (5-7.5 per second)	Slow wave focus (2-5 per second)	Slow wave focus (0.5 to 2 per second)
4. Spinal fluid total protein	0-25 mg. % Normal	25-30 mg. % Doubtful	30-40 mg. % Slightly abnormal	Over 40 mg. % Definitely abnormal
5. Mental changes	No change	Mild changes	Moderate changes	Severe changes
6. Epileptiform seizures	None	Minor spells (blackouts)	Jacksonian seizures	Grand mal or generalized seizures
7. Aphasia	None	Temporary	Moderate	Severe
8. Degree of brain damage	None or mild concussion	Contusion of brain	Penetration of brain without foreign body or presence of subdural hematoma	Severe laceration of brain with retained foreign body
9. Headaches and dizziness	None	Mild	Moderate	Severe
10. Disposition	Full duty	Limited duty	Discharged to own care	Discharged to veterans' hospital

oratory findings under each heading of open nonpenetrating, open penetrating, or closed injuries will be given.

OPEN NONPENETRATING INJURIES (20 CASES)

Frontal Lobe Injuries (right—5 cases, left—2 cases)

Some degree of unconsciousness occurred in 80 per cent of right frontal lobe injuries, but only 20 per cent were unconscious more than 24 hours. Neurologic findings were not present to any severe degree in frontal lobe injuries. Moderately severe electroencephalographic findings were present in two cases or 40 per cent of right frontal lobe injuries. There was an equal distribution of doubtful, slightly abnormal, and definitely abnormal spinal fluid total protein changes in right-sided injuries, whereas 50 per cent of the left frontal injuries had slightly abnormal spinal fluid total proteins. Three cases or 60 per cent of the right-sided lesions had mild mental changes. No epileptic seizures, aphasia, or severe brain damage was found in patients with frontal lobe injuries. Mild headaches and dizzy spells were complained of in two of the right frontal injury cases and in all of those with left frontal injuries.

All patients with open non-penetrating frontal lobe injuries were discharged in their own custody.

Left Temporal Lobe Injuries (4 cases)

Three of these cases were unconscious under one hour. Only one case (25 per cent) showed moderately severe neurologic or electroencephalographic findings. Three cases or 75 per cent had a slightly abnormal spinal fluid total protein findings. No severe or moderate mental changes or epileptic seizures were present in left temporal lobe injuries. Severe aphasia was present in one case and mild aphasia in one case of left temporal injury. All of these cases were classified as cerebral contusions. Half of the cases had mild headaches and dizzy spells. All four cases were discharged in their own custody.

Parietal Lobe Injuries (right—4 cases, left—1 case)

One of the four right parietal lobe injuries and the one case of left parietal injury were unconscious more than 24 hours. Moderately severe neurologic changes were present in only half of the right parietal lobe injuries. Two cases of right parietal injury showed severe and one case had moderate electroencephalographic changes. The left parietal lobe injury had moderate slow wave foci. In regard to spinal fluid total proteins, one case of right parietal area damage had definitely abnormal changes, whereas the left-sided injury had a doubtful spinal fluid total protein. Mild mental changes and moderate aphasia were present in only one case of the four right parietal lobe injuries. Two of the right-sided injuries had grand mal epileptic seizures, and the left parietal lobe injury had jacksonian seizures. All the parietal lobe injuries had cerebral contusions. The majority of the parietal lobe injuries complained of mild headaches and dizzy spells. Only one case of a right parietal lesion was free of symptoms. All parietal lobe injuries were discharged in their own custody.

Multilobar Injuries (4 cases)

All cases were unconscious under one hour. Moderately severe neurologic findings were present only in the left frontotemporal injury. In regard to electroencephalographic findings, the left frontotemporal and left frontoparietal in-

juries showed moderately severe slow wave foci. The left parietooccipital injury revealed a definitely abnormal spinal fluid total protein. The left frontotemporal injury had a slightly abnormal spinal fluid total protein. No mental changes or epileptic seizures were present in this group. Mild aphasia was present only in the left frontotemporal area injury. All multilobar injuries were classified as having cerebral contusions. The left frontotemporal and left frontoparietal injuries complained of moderately severe headaches and dizzy spells. All multilobar open nonpenetrating injuries were discharged in their own custody.

The most significant indications of the degree of cerebral damage in the open nonpenetrating brain injuries appeared to be as follows: Disposition (100 per cent), spinal fluid total proteins (85 per cent), duration of unconsciousness (80 per cent), degree of brain damage (75 per cent), headaches and dizzy spells (60 per cent), slow wave foci (55 per cent), neurologic findings (50 per cent), mental changes (25 per cent), aphasia (20 per cent), and epilepsy (15 per cent).

OPEN PENETRATING INJURIES (116 CASES)

Frontal Lobe Injuries (right—11 cases, left—11 cases)

Three out of 11 cases (27 per cent) of either right or left frontal lobe injuries were unconscious one to 24 hours. One case, or 9 per cent of the left frontal injuries, was unconscious more than 24 hours. One case of right frontal and one case of left frontal lobe injuries had severe neurologic findings. Three of the left frontal injuries had moderate neurologic findings, but only one case of the right-sided injuries had moderately severe neurologic signs.

Severe electroencephalographic findings were present in one case or 9 per cent of the right frontal injuries, and four cases or 36 per cent of the left-sided injuries. Moderately severe slow wave foci were seen in seven cases (64 per cent) of right frontal and five cases (46 per cent) of left frontal lobe injuries. Definitely abnormal spinal fluid total proteins were present to a fairly equal degree in this group: five right frontal (46 per cent) and six left frontal (55 per cent). Slightly abnormal total proteins were present in two left frontal injuries and two right frontal injuries (18 per cent).

One case of right frontal injury had severe mental changes. Moderately severe mental changes were seen in only one case of left frontal lobe injury. Minor or petit mal spells were present in three cases or 27 per cent of right frontal and one case or 9 per cent of left frontal injuries. Jacksonian seizures were present in one of the left frontal injuries. Two cases or 18 per cent of the left frontal lobe injuries had severe aphasia, and only one case or 9 per cent of either left- or right-sided injuries had moderate aphasia.

The left frontal injuries showed the greatest amount of brain laceration with retained foreign bodies (five cases or 45 per cent). About twice as many patients with right frontal injuries than with left frontal lobe injuries complained of moderately severe headaches and dizzy spells. It is interesting to note that no severe headaches or dizzy spells were present in this group despite rather severe brain damage. One of the patients with a right frontal lobe injury was sent to a veterans hospital for further care, and the remaining cases were discharged

in their own custody.

Temporal Lobe Injuries
(right—6 cases, left—6 cases)

Two of the left temporal and one of the right temporal lobe injuries were unconscious more than 24 hours. One-half of the right temporal injuries were unconscious one to 24 hours, whereas only one case (17 per cent) of left temporal area injury was unconscious to this degree. Three of the left temporal and one of the right temporal lobe injuries had severe neurologic findings. One case or 17 per cent of the right-sided lesions and two cases or 33⅓ per cent of the left-sided injuries had moderately severe neurologic signs.

Severe slow wave foci were about twice as frequent in right temporal as in left temporal lobe injuries, 33⅓ per cent and 17 per cent respectively. Moderately severe electroencephalographic changes were present in one-half of left-sided injuries and one-third of right-sided injuries. More definitely abnormal spinal fluid total protein changes were seen in left temporal than in right temporal lobe injuries. However, one-third of the right temporal lobe injuries showed slightly abnormal total protein changes.

Only the left temporal injuries produced either severe or moderate mental changes. Two of the right temporal injuries and one of the left temporal injuries had grand mal epilepsy. The remaining temporal lobe injuries had no epileptic seizures.

Severe aphasia was present in one-half of the left temporal lobe injuries. The degree of brain laceration with retained foreign bodies was slightly greater in the left than in the right temporal injuries; three and two cases, respectively. One case each of the right or left temporal lobe injuries complained of moderately severe headaches and dizzy spells. One patient with a right temporal lobe injury was sent to a veterans hospital. The remaining cases were discharged in their own custody.

Parietal Lobe Injuries
(right—19 cases, left—17 cases)

Three patients with right and three with left parietal lobe injuries were unconscious more than 24 hours (16 per cent and 18 per cent). However, about twice as many right parietal (seven cases) as left parietal injuries (three cases) were unconscious from one to 24 hours. There was a fairly equal distribution of severe neurologic findings in this group; four cases or 21 per cent for right parietal, and four cases or 24 per cent for left parietal lobe injuries. Moderately severe neurologic changes were seen in seven of the right parietal (37 per cent) and six of the left parietal injuries (35 per cent).

Fairly equal degrees of severe electroencephalographic changes were also present in this group; nine cases or 47 per cent of the right parietal, and seven cases or 41 per cent of the left parietal injuries. Eight right parietal (42 per cent) and eight left parietal injuries (47 per cent) revealed moderate slow wave foci.

Spinal fluid total protein changes were also present to surprisingly equal degrees, with definitely abnormal findings in six cases or 32 per cent of right and six cases or 35 per cent of left parietal lobe injuries. Slightly abnormal spinal fluid total proteins were present to a fairly equal degree in right and left parietal injuries (36 per cent and 35 per cent).

A severe mental change was found in one case (5 per cent) of right parietal injury. Moderately severe mental changes were present in two cases of right and one case of left parietal lobe injuries. Six cases or 32 per cent of the right parietal injuries, and two cases or 17 per cent of the left parietal injuries had grand mal epileptic seizures. The right motor cortex injuries had one case of jacksonian and minor seizures respectively, where as left motor cortex injuries had two cases or 12 per cent of jacksonian and no petit mal seizures.

Severe aphasia was present in four cases or 24 per cent of left parietal lobe injuries, and three cases or 18 per cent had moderate aphasia. Severe aphasia occurred in only one of the right parietal lobe injuries. Brain laceration with retained foreign bodies was present in about twice as many right parietal lesions as left parietal lobe injuries. Moderate headaches and dizzy spells were seen in three cases or 16 per cent of right parietal, and four cases or 24 per cent of left parietal lobe lesions. Four patients with right parietal lobe injuries (21 per cent) and one with left parietal lobe injuries (6 per cent) were sent to veterans hospitals. The rest were discharged in their own custody.

Occipital Lobe Injuries (right–2 cases, left–8 cases)

Three cases or 37.5 per cent of the left occipital injuries were unconscious more than 24 hours. One-half of the right occipital injuries had only mild degrees of unconsciousness. One case of the right and five cases (6 per cent) of the left occipital lobe lesions showed only mild neurologic findings. Three of the left-sided injuries had severe slow wave foci, and five cases had moderate electroencephalographic findings. One-half of those with right-sided lesions had moderate electroencephalographic abnormalities.

Exactly one-half of both right and left occipital lobe injuries had definitely abnormal spinal fluid total proteins. Left occipital lesions also had three cases or 37.5 per cent of slightly abnormal total protein findings. Moderately severe mental changes were present in 50 per cent of right occipital lobe injuries and only one case or 12.5 per cent of left-sided injuries. Only one patient with a left occipital lobe lesion had jacksonian seizures.

Mild degrees of aphasia were seen in one-half of right and one-quarter of left occipital lesions, probably due to rather extensive brain contusion and edema. One case or 50 per cent of the right occipital injuries had brain laceration with retained foreign bodies, and three cases or 37.5 per cent of left occipital area injuries had such findings.

Only mild degrees of headaches and dizzy spells were seen in this type of injury, but they were twice as common in right as in left occipital injuries. One case of left occipital lobe injury was returned to full duty. The remaining patients were discharged into their own custody.

Bilateral Injuries (frontal–5 cases, parietal–3 cases, and occipital–4 cases)

Of those with bilateral injuries, 66⅔ per cent of parietal, 60 per cent frontal, and 25 per cent occipital injuries were unconscious more than 24 hours. Unconsciousness of one to 24 hours was fairly equally distributed in this group. All the bilateral parietal injuries had severe neurologic findings, whereas only one case or 20 per cent of bilateral

frontal injuries had severe neurologic changes. One-quarter of the bilateral occipital injuries had moderate neurologic findings.

Of those with bilateral frontal injuries, 40 per cent had either severe (two cases) or moderate (two cases) electroencephalographic abnormalities. All of the bilateral parietal and one-fourth of the bilateral occipital injuries had moderate slow wave foci. One-half of the bilateral occipital injuries had normal electroencephalograms. Three cases or 60 per cent of bilateral frontal and 50 per cent of bilateral occipital injuries revealed definitely abnormal spinal fluid total proteins. Slightly abnormal protein changes were seen in one frontal, one parietal, and two occipital bilateral lesions.

Interestingly enough, severe mental changes were seen in fairly equal degrees in bilateral injuries (one case each). One-half of the bilateral occipital lesions had moderately severe mental changes. Only one case out of five of the bilateral frontal injuries had grand mal seizures. Two of the occipital lesions had minor spells.

One case or 20 per cent of bilateral frontal, and one case or 25 per cent of bilateral occipital injuries had severe aphasia. Brain laceration with retained foreign bodies was present in 60 per cent of bilateral frontal and 25 per cent of bilateral parietal injuries.

Moderate headaches and dizzy spells were seen in one frontal and two occipital bilateral injuries. Two-thirds of those with bilateral parietal injuries had only mild symptoms. Veterans Administration hospitals received one of the bilateral frontal injuries, two bilateral parietal injuries, and one bilateral occipital lobe injury. The other cases were discharged in their own custody.

Multilobar Injuries (24 cases)

Two-thirds of right parietooccipital, one-half of right frontoparietooccipital, one-third of right temporoparietal and left parietooccipital, and one-quarter of frontoparietal injuries were unconscious more than 24 hours. Unconsciousness of one to 24 hours was seen in all left temporoparietal injuries, one case or 17 per cent of left parietooccipital, one right frontoparietal, and one left frontoparietal injury (25 per cent) were unconscious one to 24 hours. Three out of four cases of right frontoparietal injury were unconscious under one hour.

Severe neurologic findings were present in three-quarters of the left frontoparietal, two-thirds of the right temporoparietal, one-half of right frontoparietooccipital, and one-quarter of right frontoparietal injuries. Two-thirds of the right parietooccipital and left parietooccipital injuries had moderately severe neurologic findings. One-half of the left temporoparietal and one-fourth of the right frontoparietal and left frontoparietal injuries also showed moderately severe neurologic findings.

All of the right frontoparietooccipital, two-thirds of the right parietooccipital, one-half of the right frontoparietal, one-third of the right temporoparietal and left parietooccipital, and one-quarter of the left frontoparietal injuries had severe electroencephalographic changes. Moderate slow wave foci were present in all left temporoparietal, four out of six of the left parietooccipital, one-half of the left frontoparietal, and one out of three of the right temporoparietal and right parietooccipital injuries. The only normal electroencephalograms were seen in one case of left frontoparietal injury and one case of right temporoparietal injury.

Definitely abnormal spinal fluid total proteins were present in all the right frontoparietooccipital injuries, two-thirds of left parietooccipital and right parietooccipital injuries, one-half of left frontoparietal and left temporoparietal injuries, and one-quarter of the right frontoparietal lesions. One-half of the left frontoparietal, one-third of right temporoparietal and right parietooccipital, one-quarter of right frontoparietal, and one-sixth of left parietooccipital injuries had slightly abnormal spinal fluid total proteins. The remaining multilobar penetrating injuries had doubtful or normal total proteins in the spinal fluid.

Severe mental changes were seen in one-half of the left temporoparietal and right frontoparietooccipital, and one-sixth of the left parietooccipital injuries. Moderately severe mental impairment was present in one-half of right frontoparietal, one-third of right parietooccipital, and one-fourth of the left frontoparietal injuries.

One case out of three of the right temporoparietal and one case out of six of the left parietooccipital injuries had grand mal seizures. Jacksonian spells were present in one-half of the left temporoparietal injuries, and minor spells were seen in one-third of the right parietooccipital injuries.

Severe aphasia was present in one-half of the left temporoparietal, one-third of the right temporoparietal and left parietooccipital, and one-quarter of the left parietooccipital injuries. Moderate aphasia was observed in 75 per cent of left frontoparietal and 50 per cent of right frontoparietal injuries. The fairly high degree of aphasia occurring in right-sided lesions could probably be explained only on the basis of widespread edema and contusion to the left as well as the right side of the brain, assuming these patients were all right handed.

Brain lacerations with retained foreign bodies were found in all right frontoparietooccipital, two-thirds of the right parietooccipital and left parietooccipital, one-half of the left temporoparietal, and one-quarter of the right frontoparietal lobe injuries.

No severe headaches or dizzy spells were complained of in the multilobar penetrating injuries. Moderate headaches and dizzy spells were seen in all left temporoparietal, two-thirds of the left parieto-occipital, one-quarter of the right frontoparietal and left frontoparietal injuries.

One of the four left frontoparietal and one of the six left parietooccipital injuries were sent to veterans hospitals. The remaining patients in this group were sent home in their own custody.

Indications of the severity of cerebral injury in the open penetrating head injuries appeared to be as follows: Degree of brain damage (100 per cent), disposition (99 per cent), electroencephalographic abnormalities (87 per cent), abnormal spinal fluid total proteins (83 per cent), duration of unconsciousness (75 per cent), neurologic findings (73 per cent), headaches and dizzy spells, (64 per cent), mental changes (46 per cent), aphasia (36 per cent), and epileptic seizures (24 per cent).

CLOSED HEAD INJURIES (64 CASES)

Frontal Injuries (right—1 case, left—1 case)

Only the one case of a right frontal injury was unconscious under one hour. No abnormal neurologic electroencephalographic findings were present in closed frontal injuries. The right frontal injury

had a definitely abnormal spinal fluid total protein and the left frontal injury had a slightly abnormal total protein. No mental changes, epileptic seizures, or aphasia were seen in this group. Both of these frontal injuries had mild contusions and both complained of moderate headaches and dizzy spells. Both were discharged in their own custody.

Left Temporal Injury (1 case)

This case was unconscious over 24 hours, but had no abnormal neurologic or electroencephalographic findings. The spinal fluid total protein was definitely abnormal. No mental changes, epileptic seizures, or aphasia were present in this case. This patient had moderate headaches and dizzy spells, and was sent home in his own custody.

Parietal Injuries
(right—7 cases, left—8 cases)

Two cases or 29 per cent of the right parietal injuries were unconscious more than 24 hours, and two cases or 25 per cent of the left parietal injuries were unconscious one to 24 hours. Severe neurologic and electroencephalographic findings were present to an equal degree in right and left parietal injuries (14 per cent). Two cases or 29 per cent of the right parietal and one case or 13 per cent of the left parietal injuries had moderate neurologic signs. Three out of seven of the right-sided lesions (43 per cent) and one-half of the left-sided injuries had moderately severe electroencephalographic changes.

Spinal fluid total proteins were definitely abnormal in four cases or 57 per cent of right parietal injuries and in four cases or 50 per cent of left parietal lesions. Slightly abnormal spinal fluid changes were also seen in two cases or 29 per cent of right parietal injuries. Severe mental changes were present in one case or 14 per cent of right parietal injuries. One-eighth of the left-sided injuries showed only moderate mental impairment.

No epileptic seizures were present in right parietal injuries, but one out of eight of the left parietal injuries had minor seizures. Moderately severe aphasia was seen in one-eighth of the left parietal injuries.

One case or 14 per cent of the right parietal injuries had a subdural hematoma, and six cases or 86 per cent had moderately severe or mild contusions. Three-quarters of the left parietal injuries had moderate or mild contusions.

Moderately severe headaches and dizzy spells were present in three cases or 43 per cent of the right parietal injuries, whereas the remaining parietal lobe closed injuries had either mild or no headaches and dizzy spells. All the cases in this group were discharged in their own custody.

Occipital Lobe Injuries
(right—3 cases, left—3 cases)

All occipital lobe closed injuries were unconscious less than one hour and only the right occipital injuries had mild neurologic findings.

Mild electroencephalographic changes were present in only one-third of the left occipital injuries. One-third of the right occipital and two-thirds of the left occipital injuries had definitely abnormal spinal fluid total proteins. The remaining one-third of the left occipital injuries had slightly abnormal spinal fluid changes. Only one of the three left occipital injuries had mild mental changes. No epileptic seizures or aphasia were present in the closed occipital injuries.

Very little evidence of brain damage

was seen in the closed occipital lobe injuries. One-third of the right occipital area injuries complained of severe headaches and dizzy spells. The remaining cases all had mild headaches and dizzy spells. All these cases were returned to full duty.

Bilateral Occipital Injuries (6 cases)

One-third of these cases were unconscious more than 24 hours, one-sixth were unconscious one to 24 hours, and one-third were unconscious less than one hour. One out of six of these cases had moderate and two out of six cases had mild neurologic findings. Severe or mild electroencephalographic changes were present in one out of six cases (17 per cent).

Two-thirds of the bilateral occipital injuries had definitely abnormal spinal fluid total proteins. One-half of these cases had mild mental changes. No epileptic seizures or aphasias were present.

Moderately severe or mild contusions were found in two-thirds of the bilateral occipital injuries. Five cases or 83 per cent of these cases had moderate headaches and dizzy spells. All bilateral occipital closed injuries were discharged into their own custody.

Temporoparietal Injuries (right—3 cases, left—3 cases)

Two-thirds of the right temporoparietal injuries and one-third of the left temporoparietal closed injuries were unconscious one to 24 hours. Only mild neurologic findings were present in one-third of the right temporoparietal and two-thirds of the left temporoparietal injuries.

Severe slow wave foci were present in the electroencephalogram of one right temporoparietal and left temporoparietal injury. One-third of the right temporoparietal and two-thirds of the left temporoparietal injuries had moderate electroencephalographic abnormalities. Exactly the same number of definitely abnormal and slightly abnormal spinal fluid total proteins were present in this group as was found for the electroencephalographic changes.

Moderately severe mental changes were found in one-third of the right and left temporoparietal injuries. No epileptic seizures were present in either group.

Severe aphasia was found only in the left temporoparietal injuries. All cases of either right or left temporoparietal closed injuries had moderately severe or mild contusions.

Two-thirds of the right temporoparietal injuries and one-third of left temporoparietal injuries complained of severe headaches and dizzy spells. One-third of the left temporoparietal injuries also complained of moderate headaches and dizzy spells. All of these cases were discharged in their own custody.

General Closed Group (28 cases)

One-fourth of this group were unconscious less than one hour. Four cases or 14 per cent had either moderate or mild neurologic findings. Moderately severe slow wave foci were present in only two of the 28 cases in this group (7 per cent).

Ten cases or 36 per cent of the general closed group had definitely abnormal and five cases or 18 per cent had slightly abnormal spinal fluid total proteins. Mild mental impairment was present in about 36 per cent of cases.

Grand mal or jacksonian seizures were present in two cases or 7 per cent of this group. Only 4 per cent had mild aphasia.

Three cases or 11 per cent of the gen-

eral closed group were classified as having moderately severe contusions, and the remaining 25 cases (89 per cent) had moderate or mild concussions. Fourteen cases or 50 per cent of this group had severe and 12 cases or 43 per cent had mild headaches and dizzy spells. Three cases (11 per cent) were returned to limited duty and the remaining 25 (89 per cent) were discharged into their own custody.

The most significant clinical and laboratory findings indicative of cerebral damage in the closed head injury group were: headaches and dizzy spells (92 per cent), disposition (91 per cent), spinal fluid total proteins (84 per cent), duration of unconsciousness (56 per cent), neurologic findings (45 per cent), brain damage (45 per cent), electroencephalographic findings (36 per cent), mental changes (34 per cent), aphasia (8 per cent), and epileptic seizures (3 per cent).

PART 2 – RELATIONSHIP BETWEEN CLINICAL AND LABORATORY FINDINGS

The second objective of this study was to determine the relationship between duration of unconsciousness, neurologic findings, electroencephalographic findings, spinal fluid total proteins, mental changes, epileptic seizures, aphasia, degree of brain damage, headaches and dizzy spells, and disposition. The number of abnormal cases and the combined direct ratio of these abnormal findings are given in table 4 for the open nonpenetrating injuries, table 5 for the open penetrating injuries, and table 6 for the closed head injuries.

Since we are dealing with the simple direct ratio between two numbers, the closest positive relationship would be 1:1, 2:2, and so on. Expressed as a whole number, the direct ratio would be the first number divided by the second number. The most perfect relationship, therefore, would be the number one. In this study the letter R is used to signify this ratio. A ratio of from 0.7 to 1.3 was considered to be evidence of positive correlation between two findings involved. Only ratios coming within this range will be discussed in order to conserve space and time.

TABLE 4

RELATIONSHIP BETWEEN ABNORMAL CLINICAL AND LABORATORY FINDINGS IN OPEN NONPENETRATING HEAD INJURIES (20 CASES)

	No. Abnormal Cases	*1* *16*	*2* *10*	*3* *11*	*4* *17*	*5* *5*	*6* *3*	*7* *4*	*8* *15*	*9* *12*	*10* *20*
1. Duration unconsciousness	16		1.6	1.5	**.94**	3.2	5.3	4	**1.1**	**1.3**	**.8**
2. Neurologic findings	10	.63		.99	.59	2	3.3	2.5	1.7	.83	.2
3. EEG findings	11	.69	**1.1**		.65	2.2	3.6	2.8	**.73**	**.92**	.55
4. Spinal fluid protein	17	**1.1**	1.7	1.5		3.4	5.7	4.3	**1.1**	1.4	**.85**
5. Mental changes	5	.31	.5	.45	.29		1.7	1.3	.33	.42	.25
6. Epileptic seizures	3	.19	.3	.27	.18	.6		.75	.2	.25	.15
7. Aphasia	4	.25	.4	.36	.24	.8	1.3		.27	.33	.2
8. Degree brain damage	15	**.94**	1.5	**1.3**	**.89**	.6	5	3.8		**1.3**	**.75**
9. Headaches, dizzy spells	12	**.75**	**1.2**	**1.1**	.58	2.4	4	3	**.8**		.6
10. Disposition	20	1.3	2	.18	.12	4	6.7	5	1.3	1.7	
% Abnormality		80	50	55	85	25	15	20	75	60	100

RELATIONSHIP OF ABNORMAL CLINICAL AND LABORATORY FINDINGS IN OPEN NON-PENETRATING HEAD INJURIES (TABLE 4)

There were no severe neurologic findings, mental changes, or headaches and dizziness in this group of 20 open non-penetrating head injuries. The greatest severity of brain damage was classified as contusion of the brain. All cases in this group were discharged in their own custody.

The closest relationship between the duration of unconsciousness and other findings was seen in the degree of brain damage ($R = 1.1$), the spinal fluid total protein ($R = .94$), headaches and dizzy spells ($R = 1.3$), and the disposition ($R = .8$).

The nearest relationship was present between abnormal neurologic findings and abnormal electroencephalographic changes ($R = .99$). A fairly positive ratio existed between neurologic findings and the headaches and dizzy spells ($R = .83$).

A fairly close relationship existed between electroencephalographic findings and neurologic abnormalities ($R = 1.1$). When electroencephalographic findings were compared to the headaches and dizzy spells, the ratio was .92. The ratio of electroencephalographic findings to the degree of brain damage was .73 and to the duration of unconsciousness .69.

There was a fairly close relationship between the spinal fluid total protein and the duration of unconsciousness and degree of brain damage ($R = 1.1$). Another fairly positive ratio existed between the spinal fluid total protein and the disposition ($R = .85$).

The only close relationship seen between the degree of mental changes and other findings was in aphasia ($R = 1.3$).

No significantly close relationship existed between epileptic seizures and any of the other clinical or laboratory findings except aphasia ($R = .75$). The presence of aphasia did not seem to have a positive relationship with any other factors studied except epilepsy ($R = .8$) and mental changes ($R = 1.3$).

There was a fairly close correlation between the degree of brain damage and the duration of unconsciousness ($R = .94$), the spinal fluid total protein ($R = .89$) and the electroencephalographic findings ($R = 1.3$), headaches

TABLE 5
RELATIONSHIP BETWEEN ABNORMAL CLINICAL AND LABORATORY FINDINGS IN OPEN PENETRATING HEAD INJURIES (116 CASES)

	No. Abnormal Cases	*1* *87*	*2* *85*	*3* *101*	*4* *96*	*5* *53*	*6* *28*	*7* *42*	*8* *116*	*9* *73*	*10* *99*
1. Duration unconsciousness	87		**1.02**	**.86**	**.92**	1.6	3.1	2.1	**.75**	**1.2**	**.89**
2. Neurologic findings	85	**.98**		**.84**	**.89**	1.6	3	2	**.73**	**1.2**	**.86**
3. EEG findings	101	**1.1**	**1.2**		**1.1**	1.9	3.6	2.4	**.86**	1.4	**1.02**
4. Spinal fluid protein	96	**1.1**	**1.1**	**.95**		1.8	3.4	2.3	**.83**	**1.3**	**.97**
5. Mental changes	53	6.1	6.2	.52	.55		1.9	1.3	.46	.73	.53
6. Epileptic seizures	28	.32	.31	.28	.29	.52		.67	.24	.39	.28
7. Aphasia	42	.48	.49	.42	.44	.79	1.5		.36	.58	.43
8. Degree brain damage	115	**1.3**	1.4	**1.1**	**1.2**	2.2	4.2	2.8		1.6	**1.2**
9. Headaches, dizzy spells	73	**.84**	**.86**	**.72**	**.76**	1.4	2.6	1.7	.63		.64
10. Disposition	99	**1.1**	**1.2**	**.98**	**1.03**	1.9	3.4	2.4	**.85**	1.4	
% Abnormality		75	73	87	83	46	24	36	100	64	99

and dizzy spells (R = 1.3), and the disposition (R = .75).

A positive relationship existed between headaches and dizzy spells and electroencephalographic findings (R = 1.1). The ratio of headaches and dizzy spells to neurologic findings was 1.2, and to the degree of brain damage. 0.8. There was also a fairly close relationship of these symptoms to the duration of unconsciousness (R = .75).

All cases of open nonpenetrating injuries were discharged in their own custody, since they were not considered well enough to return to full or limited duty or not disabled enough to be sent to a veterans hospital. The closest relationship between the disposition and other findings was in the degree of brain damage (R = 1.3) and the duration of unconsciousness (R = 1.3).

From this data it is concluded that the closest correlations with other findings in the open nonpenetrating head injuries were present in the degree of brain damage, headaches and dizzy spells, spinal fluid total protein, electroencephalographic findings, and the duration of unconsciousness.

RELATIONSHIP OF ABNORMAL CLINICAL AND LABORATORY FINDINGS IN OPEN PENETRATING HEAD INJURIES (TABLE 5)

The duration of unconsciousness had significantly close relationships to the neurologic findings (R = 1.02), the spinal fluid total protein (R = .92), disposition (R = .89), electroencephalographic findings (R = .86), degree of brain damage (R = .75), and headaches and dizzy spells (R = 1.2). The neurologic findings had nearly the same positive relationship to other clinical and laboratory findings as the duration of unconsciousness.

There was a fairly close relationship between abnormal electroencephalographic findings and the disposition (R = 1.02), duration of unconsciousness (R = 1.1), spinal fluid total protein (R = 1.1), neurologic findings (R = 1.2), and the degree of brain damage.

The spinal fluid total protein changes had nearly the same positive relationship to the other findings as the duration of unconsciousness, except that there was a slightly closer relationship between the spinal fluid total protein and electroencephalographic findings (R = .95).

TABLE 6
RELATIONSHIP BETWEEN ABNORMAL CLINICAL AND LABORATORY FINDINGS IN CLOSED HEAD INJURIES (64 CASES)

	No. Abnormal Cases	*1* *36*	*2* *29*	*3* *23*	*4* *54*	*5* *22*	*6* *3*	*7* *6*	*8* *29*	*9* *59*	*10* *58*
1. Duration unconsciousness	36		1.3	1.6	.67	1.6	12	6	1.2	.61	.62
2. Neurologic findings	29	**.81**		**1.3**	.54	1.3	9.7	4.8	**1**	.49	.5
3. EEG findings	23	.64	**.79**		.42	**1.04**	7.6	3.8	**.79**	.38	.39
4. Spinal fluid protein	54	1.5	1.8	2.3		2.4	18	9	1.8	.91	.93
5. Mental changes	22	.61	**.75**	**.95**	.41		7.3	3.7	**.75**	.37	.38
6. Epileptic seizures	3	.08	.10	.13	.06	.13		.5	.10	.05	.05
7. Aphasia	6	.17	.21	.26	.11	.27	2		.21	.10	.10
8. Degree brain damage	29	**.81**	**1**	**1.2**	.54	**1.3**	9.9	5		.49	.5
9. Headaches, dizzy spells	59	1.6	2	2.6	1.1	2.7	19.7	9.8	2		1.02
10. Disposition	58	1.6	2	2.5	1.1	2.6	19.3	9.7	2	.98	
% Abnormality		56	45	36	84	34	3	8	45	92	91

The only significantly close relationship found in the mental changes was between this factor and headaches and dizzy spells (R = .73) and aphasia (R = 1.3). There was no positive relationship between epileptic seizures and the other clinical or laboratory findings in the open penetrating head injuries.

Aphasia showed a close relationship to mental changes (R = .79). The degree of brain damage had significantly close relationships to electroencephalographic findings (R = 1.1), spinal fluid total protein (R = 1.2), disposition (R = 1.2), and the duration of unconsciousness.

There was a fairly positive ratio between headaches and dizzy spells and the neurologic findings (R = .86), duration of unconsciousness (R = .84), the spinal fluid total protein (R = .76), and electroencephalographic findings (R = .72).

Of the cases with open penetrating head injuries 11 per cent were sent to Veteran Administration hospitals, one case was sent to full duty, and the rest were discharged in their own custody. The abnormal findings determining discharge of a patient to a veterans hospital or his own home appeared to be the electroencephalographic findings (R = .98), the spinal fluid total protein (R = 1.03), the duration of unconsciousness (R = 1.1), the degree of brain damage (R = .85), and the neurologic findings (R = 1.2).

From this data it appears that the closest relationships in the open penetrating injuries existed between the various clinical and laboratory findings in the duration of unconsciousness, the neurologic findings, the spinal fluid total proteins, disposition, and the electroencephalographic changes.

RELATIONSHIP OF ABNORMAL CLINICAL AND LABORATORY FINDINGS IN CLOSED HEAD INJURIES (TABLE 6)

The only fairly close relationship between the duration of unconsciousness and other findings was in the degree of brain damage (R = 1.2) and the neurologic findings (R = 1.3).

Abnormal neurologic signs had a perfect ratio of 1 to the degree of brain damage. Other fairly close relationships of the neurologic findings were seen in the duration of unconsciousness (R = .81), the electroencephalographic findings (R = 1.3), and mental changes (R = 1.3).

There was almost a perfect ratio of 1.04 between the electroencephalographic findings and mental changes. The electroencephalographic findings compared to the neurologic changes and to the degree of brain damage was 0.79.

As far as the spinal fluid total protein changes were concerned, there was only a fairly close relationship with the disposition (R = .93) and headaches and dizzy spells (R = .91).

Mental changes showed the closest relationship to the electroencephalographic findings (R = .95). The mental changes showed a ratio of 0.75 to the neurologic changes and the degree of brain damage.

Epileptic seizures and aphasia bore no close relationship to any of the other clinical or laboratory findings. The degree of brain damage had the closest direct ratios to the neurologic findings (R = 1), duration of unconsciousness (R = .81), electroencephalographic findings (R = 1.2), and mental changes (R = 1.3).

A fairly close correlation existed between headaches and dizzy spells and the disposition (R = 1.02) and the spinal

fluid total protein findings ($R = 1.1$). Disposition showed a close relationship to headaches and dizzy spells ($R = .98$) and to the spinal fluid total proteins.

In the closed head injuries, the greatest number of close relationships existed between the various findings in the following order: degree of brain damage, neurologic findings, electroencephalographic findings, and mental changes.

SUMMARY AND CONCLUSIONS

A study of 200 head injuries consisting of 20 cases of open nonpenetrating injuries, 116 cases of penetrating injuries, and 64 cases of closed head injuries has been presented.

Part 1 of this paper is an analysis of the results of the duration of unconsciousness, neurologic signs, electroencephalographic findings, mental changes, epileptiform seizures, aphasia, degree of brain damage, headaches and dizzy spells, and disposition in these 200 head injuries according to the region of the brain injured. These clinical and laboratory findings are graded as no change, mild, moderate, or severe changes.

The areas of the brain showing the most severe degrees of clinical and laboratory changes in the open nonpenetrating injuries were the right parietal, left frontal, left temporal, and left frontotemporal areas.

In the open penetrating injuries, right and left parietal, left temporal, left frontal, left occipital, bilateral frontal and occipital, and the multilobar parietal lobe injuries appeared to be the most severe.

The areas of the brain having the most severe changes in the closed injuries were the right and left parietal, left temporal, bilateral occipital, and the multilobular areas.

The most significant clinical and laboratory findings indicative of cerebral damage in these 200 head injuries were the disposition, spinal fluid total protein, duration of unconsciousness, the electroencephalographic changes, degree of brain damage, neurologic findings, and headaches and dizzy spells. It was noted that headaches and dizzy spells occurred more often in closed than open head injuries. The electroencephalographic findings were more severe in the open penetrating injuries, and the number of epileptic seizures was greater in this type of injury.

Part 2 of this study is an analysis of relationships between the various clinical and laboratory findings. The closest relationships existing between the abnormal findings in the open nonpenetrating injuries was found in the degree of brain damage, disposition, headaches and dizzy spells, spinal fluid total proteins, electroencephalographic findings, and the duration of unconsciousness.

The most positive relationships in the open penetrating injuries existed in the duration of unconsciousness, the neurologic findings, the spinal fluid total proteins, disposition, and the electroencephalographic changes.

The closed head injuries showed the closest correlations of the degree of brain damage, the neurologic findings, the electroencephalographic changes, and the mental changes.

In the original statistical analysis of these 200 head injuries, each degree of impairment under each of the clinical and laboratory findings was determined and correlated with each other. These correlations were originally computed by the use of a punch card system. However, because of the great amount of

figures and correlations involved, it was decided to limit this paper to the results of the total or most abnormal findings under each type of head injury.

This study was begun under the inspiration and guidance of the former chief of the Cushing General Hospital neurologic service, the late Dr. Frederick H. Lewey.
Grateful acknowledgment is also made to Dr. Henry L. Sisk, who made many of the original calculations and did all the mental or personality tests included in this study.

■ Long after this first publication, Sir Charles brought forward several facts, experimental and pathological, showing that the nervous conductors for motion are distinct from those for sensation. He showed that the facial nerve is motor, and that the ganglionic root of the trigeminal is for sensation. But although these facts had given good grounds to the hypothesis that the posterior or ganglionic roots of the spinal nerves are used for sensation, while the anterior roots are for motion, positive evidences of the exactitude of this distinction were still wanted. To Mr. Magendie belongs the merit of having furnished the proofs that were needed. He showed that the section of all the posterior roots of the nerves of one limb destroys the sensibility in the limb, while a section of the anterior roots of the nerves of a limb abolishes voluntary movements, leaving sensibility unaltered. He also found that strychnia, in this last case, does not excite convulsions in the paralyzed limb, while there are convulsions, in the limb deprived of sensibility, after the section of the posterior roots. So far as these experiments alone are studied, it seems quite certain that the anterior roots are motor and not sensitive, and that the posterior roots are sensitive and not motor; but Magendie tried other experiments, and, not being aware of a singular fact, which he discovered only in 1839, he arrived at conclusions which were quite different from those just exposed. The irritation of the anterior roots he found evidently to induce pain, though in a less degree than that of the posterior. On another side he found sometimes that local movements took place when he irritated the posterior roots. Here, then, are two facts which seem in direct opposition to the theory of Sir Charles Bell.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Volume 5 Neurology *Number 5*

Editorial . . .

IN ACCEPTING ARTICLES for publication in *Neurology*, an attempt has been made to place emphasis on clinical contributions, especially those dealing with the therapeutic aspects of organic diseases of the nervous system. It is obvious, however, that one cannot divorce the clinical from the investigative aspects of medicine, and we have always welcomed original research papers, especially if they appear to have a definite application, either directly or indirectly, to clinical neurology. Without recourse to and assistance from the sciences basic to the study of disease of the nervous system, our specialty can make no progress.

Neurology is an expanding discipline, and it must not be limited by arbitrary boundaries – it must reach out beyond its customary confines. Neuroanatomic and electrophysiologic studies on the effects of stimulation and destruction of both cortical and deeper areas of the brain have brought back the realization that the brain is actually the organ of the mind. Furthermore, recent investigation into the neurophysiologic and neuropharmacologic aspects of mental disease is confirming what so many of us have believed for so long, but were reluctant to express too definitely – that in many, at least, of the so-called functional disorders there is a basic disturbance of the physiology of certain neural centers. It is now more apparent than ever that electrophysiologic, neurochemical, and pharmacologic investigations of the cortex, the hypothalamus, the diencephalon, the reticular formation, and related structures will throw new light on the biologic basis of behavior.

The fact that hallucinations and disturbances of emotions, memory, and behavior may be produced by drugs and that these manifestations may be prevented or relieved by other drugs expands the study of the nervous system and the brain into new and provocative fields. In this issue of *Neurology* we are publishing an article, written by the president of the American Academy of Neurology, on the neurochemical changes in abnormal mental states, with a lead toward the relief of the latter. This very novel and stimulating piece of clinical investigation would probably not be considered to be within the confines of the field of neurology, if one regards the latter in the usually constricted sense of the term. If, however, one believes, as we feel one should, that our specialty should deal with all of the morphologic and physiologic alterations that affect the nervous system – a study of the entire nervous system in health and disease – then this article is concerned with neurology in its broadest sense.

R. N. D.

DIAGNOSTIC NOTE

Photographic Detection of Unilateral Masking in Parkinsonism

W. James Gardner, M.D. and Thomas J. Lannon

THE DIAGNOSIS of parkinsonism is frequently missed in its early unilateral phase. This is particularly true when tremor is absent. In these cases, masking of the features is difficult to recognize because it is obscured by the normal expression of the opposite half of the face. The following has proved to be a reliable method of demonstrating unilateral masking.

METHOD

A full-face photograph of the patient is taken and two regular prints are made. The negative is then reversed and a mirror-image or reverse print is made. One of the regular prints and the reverse print are cut down the middle. Composite photographs are assembled by matching both left halves and both right halves of the prints. Figures 1 and 2 demonstrate the results: in both, *A* is the regular full-face photograph of the patient; *B* is the composite of the two right halves of the face; *C* is the composite of the two left halves of the face. Little more than a passing glance is required to detect the difference of expression on the two sides.

FIG. 1. Suspected right unilateral parkinsonism. *A*. Full-face view. *B*. Composite of the right side of face demonstrating early masking. *C*. Composite of left side of face showing normal expression.

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FIG. 2. Early left unilateral parkinsonism. The symptoms in this patient's left arm previously had been attributed to a lesion of the brachial plexus. *A*. Full-face view. *B*. Composite of right side of face showing normal expression. *C*. Composite of left side of face showing definite masking.

■ It seems very probable that there is at least a part of the sensations giving to the mind the idea of the state of a muscle, which passes along the anterior roots to go to the sensorium. But, although I agree so far with Arnold, I do not admit with him that it is only through the anterior roots that impressions are conveyed from the muscles to the brain. When a galvanic current is applied to the muscles of a limb of a frog, on which the posterior roots of the nerves of this limb have been divided, no trace of pain is produced, and all the other causes of pain are also unable to cause it, when applied either to the skin or to the muscles. When I examine, in another lecture, the correlation of pathological cases with experimental facts, I will speak again of the views of Arnold. I dismiss actually the subject, contenting myself in saying that, even if muscles have peculiar nerve-fibres, which go up to the brain along the anterior roots, to give there some special sensations in correspondence with the degree of contraction, it seems nevertheless quite certain that the nerves of touch and those which convey painful impressions do not pass by the anterior roots, and that, therefore, the theory of Sir Charles Bell, as regards these nerves, remains entire.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Primary Atypical Pneumonia with Associated Encephalomyelitis

Robert B. Jackson, M.D.

PRIMARY ATYPICAL PNEUMONIA is not commonly considered to have accompanying neurologic abnormalities, though associated headache frequently occurs. Pathologic reports in fatal cases record essentially no abnormalities of the central nervous system.

A patient in whom the diagnosis of primary atypical pneumonia seems quite tenable, who had signs and symptoms of a concomitant encephalomyelitis, is reported herein.

Twenty-seven instances of pulmonary infection diagnosed as primary atypical pneumonia showing associated central nervous system abnormalities have been found in reviewing the literature. The majority of these instances are certainly subject to challenge regarding the diagnosis of primary atypical pneumonia, though some, with scattered pulmonary infiltration shown by x-ray, a relative leukopenia, and elevated cold agglutinin or Streptococcus MG titers, seem fairly definite. The central nervous system abnormalities reported may be grouped as follows: myelitis, seven (two fatalities); encephalitis, six (one fatality); meningitis, six; Guillain-Barré syndrome, one; encephalopathy, two; polyneuritis, two; and meningismus, three. Literature covered in the review of this subject appears in the appended list of references.

CASE REPORT

A 40 year old man was admited to the neurology service of the Veterans Administration Hospital, San Francisco, on January 30, 1954, because of weakness and numbness of the legs for three days. For about a month prior to admission he had had a cold with possibly some fever, and a cough productive of whitish sputum which was at times blood-streaked. Four days before admission he developed diffuse myalgia, and the next day noted a numb feeling in his legs. A day later his legs began to feel weak and he was unable to void. The numbness ascended to the level of the upper abdomen by the time of admission and the leg weakness had progressed until he was unable to walk. There was no history of previous neurologic difficulty, visual complaints, or symptoms referable to the arms. He had experienced no pain except for occipital headache on coughing or flexing his neck.

Physical examination at the time of admission showed the following: blood pressure 115/75, pulse 68, temperature 99.5, and respirations 20. The patient was a well developed and well nourished Mexican appearing moderately acutely ill. He was alert and cooperative, but was unable to sit up because of weakness. The skin was unremarkable and there was no lymphadenopathy. There was equivocal nuchal rigidity. The lungs were resonant without rales or rhonchi. The heart and abdomen were within normal limits. The bladder was not distended. Rectal examination was not remarkable.

Neurologic examination revealed no papilledema and the pupils were normal. Extraocular muscles were unimpaired and there was no

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nystagmus. Facial sensation was normal. There was an equivocal weakness of the lower half of the right side of the face. The remainder of the cranial nerves were normal. There was a flaccid paresis of both legs, most marked at the hips and knees. The patient was unable to raise his legs against gravity. There was no evident weakness of the arms. There was no muscular wasting and no fasciculations were seen. There was complete loss of perception of all sensory modalities below the level of T-10 dermatome, and impaired sensory perception between T-7 and T-10 levels. The deep muscle reflexes were hypoactive but symmetrical in the arms and normally active and symmetrical in the legs. The superficial abdominal and cremasteric reflexes were absent. There was no Babinski sign.

Laboratory data: White cell count on admission was 11,600 with 68 per cent polymorphonuclear cells. Chest x-ray showed patches of infiltration at the left base suggestive of an inflammatory process. Blood culture revealed no growth. Urinalysis and blood serology were not remarkable. Lumbar puncture revealed an initial pressure of 198 mm. The fluid was clear and colorless. There were 101 lymphocytes per cu. mm. Protein was 58 mg. per cent with a positive Pandy test. Spinal fluid serology was negative. Gold curve was 0122242100.

Numerous bacteriologic studies were performed in an effort to identify a causative agent of the patient's illness. The only positive finding in this regard was a consistently elevated cold agglutinin titer which was reported the day after admission as 3 plus in greater than 1:1024 dilution. Over the subsequent four months this titer gradually fell to a level of 1 plus at a dilution of 1:128. Negative bacteriologic reports included appropriately paired blood specimens or cultures for: western equine encephalitis, St. Louis encephalitis, mumps, Q fever, infectious mononucleosis, lymphocytic choreomeningitis, coccidioidomycosis, influenza A and B, Japanese B encephalitis, brucellosis, psittacosis, lymphopathia, granuloma venereum, leptospirosis, and tuberculosis. Routine spinal fluid cultures were negative. Urine tests for porphyria were negative.

Course: During the first two days after admission the patient's legs became completely paretic and his sensory level rose to T-4 dermatome. He developed definite nuchal rigidity and the right lower facial weakness became more definite. He became irritable and lethargic, but was never disoriented. Deep muscle reflexes in the legs became completely absent, and after two days of hospitalization bilateral Babinski signs were present. His condition then remained stable for a few days, after which he began to improve slowly. After admission he was given penicillin and Aueromycin daily, but he did not become afebrile for two and a half weeks. Deep muscle reflexes in the legs slowly returned over the next few weeks and the sensory level gradually descended. Urinary retention persisted for seven weeks, after which it was possible to discontinue an indwelling catheter. Along with the return of reflexes and descent of the sensory level, motor function was slowly regained. This gradual improvement continued and during this period the patient received active and passive physiotherapy. A second lumbar puncture performed five days after admission revealed a normal protein, 33 lymphocytes, and 2 polymorphonuclear cells. Two subsequent lumbar punctures were within normal limits, the last being performed four months after the onset of illness.

The patient at no time showed any physical findings suggesting a pulmonary infiltration to correlate with the x-ray findings. A chest x-ray ten days after admission showed clearing of the density at the left base. Skull and spine x-rays were normal. An electrocardiogram obtained shortly after admission was normal. Electroencephalograms done during the first week, the second month, and fourth month after admission were normal. Electromyography four months after admission showed scattered fibrillation potentials in the right gastrocnemius muscle.

Neurologic findings four months after admission revealed a slight right lower facial weakness, ability to walk well without support, no evidence of muscular wasting, normal sensory perception for all modalities, deep muscle reflexes symmetrically normal in the arms and legs, normal superficial abdominal and cremasteric reflexes, and a right Babinski sign.

Forty cases admitted to this hospital since 1945 having a final diagnosis of primary atypical pneumonia were reviewed. Twenty-three of these cases were tested for cold agglutinins, and six showed significant elevations. One case with elevated cold agglutinins exhibited nuchal rigidity and headache but had a normal spinal fluid, and another case in whom cold agglutinins were not obtained had equivocal nuchal rigidity. None of the remaining 38 patients were described as having neurologic symptoms or signs.

DISCUSSION

A diagnosis of primary atypical pneumonia in this patient seems to be appropriate in view of the presence of fever, cough,

pulmonary infiltration by x-ray, white cell count of 11,600, and a definite elevation of cold agglutinin titer which gradually diminished during convalescence. The associated central nervous system infection might best be termed a meningoencephalomyelitis, there having been nuchal rigidity, lethargy, irritability, right lower facial weakness, and signs of disseminated spinal cord involvement. The exact etiology of this condition is of course unknown in this patient, but the explanation would seem to be an invasion of the central nervous system by the same agent involved the lungs, that is, the virus of primary atypical pneumonia.

SUMMARY

Nervous system complications in primary atypical pneumonia are rare and when they do occur may range from mild meningeal signs to a fatal encephalomyelitis. A case report of a patient with primary atypical pneumonia with a concomitant meningoencephalomyelitis is presented.

The author wishes to express his appreciation for the encouragement and helpful advice of Dr. Walter J. Friedlander, chief of neurology and psychiatry section, Veterans Administration Hospital.

REFERENCES

1. Goldstein, R.: Myelitis after atypical pneumonia, Helvet. paediat. acta 8:107, 1953.
2. Scadding, J. G.: Disseminated focal pneumonia, Brit. M. J. 2:956, 1937.
3. Campbell, T. A., Strong, P. S., Grier III, G. S., and Lutz, R. J.: Primary atypical pneumonia, J.A.M.A. 122:723, 1943.
4. Sheppe, W. M., Osterman, A. L., Ahroon, C. R., and Zuflacht, J. J.: Meningomyelitis, a complication of primary atypical pneumonia, J.A.M.A. 122:1245, 1943.
5. Perrone, H., and Wright, M.: A fatal case of atypical pneumonia with encephalitis, Brit. M. J. 2:64, 1943.
6. Gundersen, S.: Primary atypical pneumonia of unknown etiology, New England J. Med. 231:697, 1944.
7. van Ravenswaay, A. C., Erickson, G. C., Reh, E. P., Siekierski, J. M., Pottash, R. R., and Gumbiner, B.: Clinical aspects of primary atypical pneumonia, J.A.M.A. 124:1, 1944.
8. Glendy, R. E., Beaser, S. B., and Hankins, W. D.: Primary atypical pneumonia of unknown cause with unusual manifestations and complications, Arch. Int. Med. 75:30, 1945.
9. Turner, R. W. D.: Atypical pneumonia, Lancet 1:493, 1945.
10. Holmes, J. M.: Neurological complications in atypical pneumonia, Brit. M. J. 1:218, 1947.
11. Suchett-Kaye, A. I.: Acute transverse myelitis complicating pneumonia, Lancet 2:417, 1948.
12. Keizer, D. P. R.: Neurologic complications in primary atypical virus pneumonia of children, Maandschr. kindergeneesk. 17:126, 1949.
13. Amsterdam, B.: Viral pneumonitis of unknown cause with unusual neurologic complications—report of two cases, New York J. Med. 50:593, 1950.
14. London, S., and Laven, H.: Transverse myelitis complicating primary atypical pneumonia with recovery following chloromycetin therapy, New York J. Med. 51:787, 1951.
15. Chang, Hsioh-Teh: Studies on primary atypical pneumonia in Peking, Chinese M. J. 69:435, 1951.

■ The idea first proposed by Bell was, that the posterior columns of the spinal cord are the continuations of the posterior roots, and that they convey the sensitive impressions to the brain. He thought also that the anterior columns convey the orders of the will to muscles. This theory received no other support from its author than the following attempt at experimenting, which we record in the words of Sir Charles: "I found that injury to the anterior portion of the spinal marrow convulsed the animal more certainly than injury to the posterior portion; but I found it difficult to make the experiment without injuring both portions."

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Cerebral Infarction in Migraine

James Peter Murphy, M.D.

MIGRAINE is a disease of unproved etiology, in which vasoconstriction of intracranial arteries often precedes or accompanies dilatation of extracranial arteries. During the preliminary vasospastic phase of an attack of migraine, contraction of the ophthalmic artery causes the subjective phenomena of scintillating scotomata, "fortification spectra," or actual blindness. In many afflicted individuals, major arteries of the cerebral circulation likewise go into spasm; hence the familiar migrainous homonymous hemianopia due to constriction of the posterior cerebral artery with ischemia of the occipital cortex. Unusually hemiplegia, hemiparesis, hemianesthesia, paresthesia, hallucinatory experiences, or aphasia may usher in an attack of migraine or can constitute the episode in entirety. Increasing dilatation of the extracranial arteries (temporal, frontal, or occipital) soon follows and the incapacitating hemicranial headache, which is the outstanding clinical feature of migraine, results.

In the majority of migraine patients who exhibit signs of cerebral deficit in the incipiency or at the height of attacks, the neurologic phenomena are of brief duration no matter how often repeated and restitution to normal is rapid and complete. Indeed, it is for this reason that the etiology of the cerebral manifestations of migraine may be confidently stated to be intracranial arteriospasm. In many of these individuals, marked asymmetry of amplitude in the electroencephalogram, low potentials being found in one occipital or temporal area, undoubtedly is subtle evidence of permanent brain injury as an aftermath of temporary ischemia not otherwise manifest. The high incidence (over 50 per cent of cases) of moderately but generally abnormal electroencephalograms in all migraine patients may or may not be the result of repetitious cortical anoxia. It is more likely that such electroencephalographic abnormality confirms the suspicion of relationship of certain types of migraine to the epileptic state.

It is not generally known that serious and permanent neurologic crippling may be the residual of a migraine attack in rare instances, but, this has been reported previously. Permanent occlusion of the central artery of the retina has been observed to follow repeated spasm of a vessel presumed to be also sclerosed. Autopsy verification of cerebral infarction without discoverable vascular thrombosis and of fatal cerebral hemorrhage without visible rupture of an

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artery or congenital aneurysm has been reported by Dunning.[1] The objection may be raised that these patients suffered not only from migraine but also from another cerebrovascular disorder; one can only assay the evidence and question or accept the conclusions.

The following case report concerns an instance of cerebral infarction in a young patient, a sufferer from migraine for many years, following a series of typical migrainous attacks. In this case there is no evidence of any type of organic vascular disease, generalized or cerebral.

REPORT OF CASE

A 36 year old white woman was first examined at the Suburban Hospital, Bethesda, Maryland on January 24, 1954. This patient had been subject to severe and incapacitating attacks of migraine since girlhood. The typical onset of a seizure occurred with scintillating scotomata or dimness of vision in the left eye, followed by hemicrania usually also on the left. Over a period of years the visual acuity of the left eye had become reduced. Shortly before admission to the hospital the patient experienced a bout of recurrent and especially severe headaches, closely spaced, and preceded by complete loss of vision in the left eye. Following the last attack of this nature she suddenly developed right hemiplegia, complete amblyopia on the left, and an almost global aphasia.

The blood pressure was 140/70 and the pulse 80. Peripheral arterial pulsations were excellent, including those of both internal carotid arteries (pharyngeal palpation). The temperature was normal, as were the blood count and urinalysis. The patient was fairly alert and pleasant although slightly confused. The neck was limber and Kernig signs were absent. Papilledema or retinal hemorrhages were not observed in either ocular fundus. The left eye was blind and the optic nerve was yellow-white and atrophic. The temporal field of vision of the right eye was absent (threatening gestures). There was an almost complete hemiplegia on the right, sparing the face and with preservation of some motion in the leg. The Babinski sign was present, abdominal reflexes were absent on the right, and tendon reflexes were depressed. Deep and superficial sensations were present but reduced. Motor and sensory reactions on the left were normal. Vocalization was confined to grunts or expressions of acquiescence; there was evidently no speech comprehension. Spinal puncture revealed an initial fluid pressure of 180 mm. of water (patient relaxed); the protein content of the clear specimen was 49 mg. per cent; no cells were seen microscopically. Blood and cerebrospinal fluid serologic tests were negative for syphilis.

Left stellate block resulted in almost immediate but only partial restoration of vision in the left eye (recognition of fingers and primary colors) and slight movement in the right arm. Speech likewise improved somewhat. Roentgenograms of the skull disclosed what appeared to be erosion of the posterior clinoid processes of the sella turcica. This finding, in addition to what was thought to be an insufficient response to stellate block, prompted transfer of the patient to the George Washington University Hospital for purposes of electroencephalographic examination and other diagnostic studies relevant to the possibility of intracranial tumor.

An electroencephalogram disclosed a "focus of high voltage slow activity appearing intermittently in bursts in the left frontotemporal area, compatible with left frontal glioma or abscess" (figure 1). Accordingly, a carotid arteriogram was performed on the left. Films revealed absence of filling of the anterior cerebral artery in any phase of the angiogram, and the middle cerebral artery appeared to be displaced slightly inferiorly and downward. Following arteriography hemiplegia again became profound. In view of the slight elevation of spinal fluid pressure and protein content and the presumably abnormal roentgenographic findings, it was decided to proceed with an exploratory operation. On January 28, 1954 a left frontotemporal craniotomy was performed. The brain was of normal appearance externally; nonetheless, the cortex was transected and the region of the internal capsule was approached. Just external to the head of the caudate nucleus the white matter was soft and slightly yellow in color. A biopsy specimen obtained was reported as normal cerebral tissue. Neoplastic or inflammatory material was not encountered. Stellate block was repeated postoperatively.

Convalscent improvement was rapid and gratifying. By April 1954 the patient was able to type and play the piano and attempted a return to her usual secretarial duties. Slight impairment of memory and defects of judgment precluded continuance of employment, and at present she is taking a course of instruction in office practice. An electroencephalogram made on August 31, 1954 was only mildly abnormal in the left frontotemporal region and was

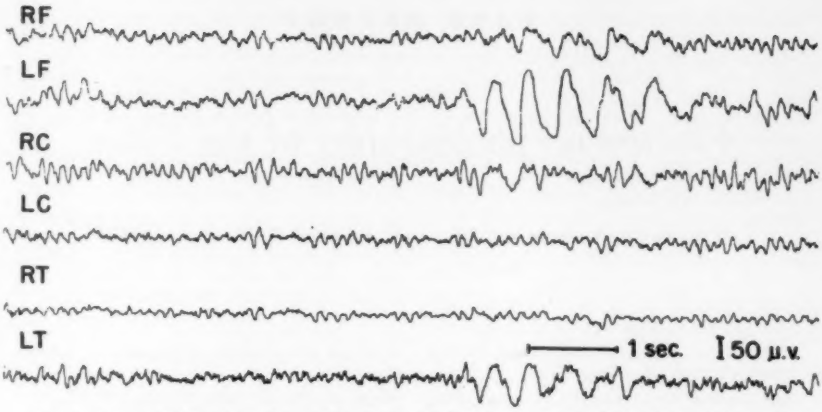

FIG. 1. Bursts of high voltage slow activity in the left frontal and temporal leads of the electroencephalogram in a case of cerebral infarction in migraine.

greatly improved as compared with the preoperative tracing. Physical examination on September 29, 1954 revealed slight amnestic nominal aphasia, restoration of visual acuity in the left eye to the status existing before hemiplegia, minimal hyperreflexia on the right, and no other neurologic abnormalities. Interestingly, there have been no further attacks of migraine, although previously they occurred at least monthly. The primary trunks of the superficial temporal and middle meningeal arteries were spared at operation.

SUMMARY

On the basis of persistent intracranial arteriospasm associated with the migraine syndrome, this case is considered to be one of cerebral infarction. Optic atrophy is likewise believed to be the residual of recurrent vasoconstriction of the ophthalmic artery on the same side as the stroke.

REFERENCE

1. DUNNING, H. S.: Intracranial and extracranial vascular accidents in migraine, Arch. Neurol. & Psychiat. 48:396, 1942.

■ Every muscular contraction seems to generate a galvanic excitation of the sensitive nerves in the neighborhood of the muscular fibres; and, the degree of excitation being in proportion to the degree of energy of the contraction, we have, in this way, an excellent means of judging of the state of the muscles. When the contraction acquires the degree which it has in cramps, then it causes pain, which is also in proportion to the energy of the spasm. If we succeed when we have a cramp in making it cease by elongating the contracted muscle, we find that the pain often increases at first, and disappears only when the contraction has ceased.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Electroencephalography of the Fetus

Winslow J. Borkowski, M.D. and Richard L. Bernstine, M.D.

A STUDY has been undertaken at Jefferson Medical College Hospital to investigate intrauterine fetal physiology, including examination of the functional development of the fetus. This report presents the records of brain activity from two fetuses.

The specimens were obtained from abdominal section. The older fetus was removed together with the uterus (abdominal hysterectomy). The other fetus was obtained from an early tubal pregnancy. Both specimens were placed in towels soaked with warm (37° C.) normal salt solution and immediately removed to the laboratory. All recordings were made with needle electrodes and recorded on a standard Grass eight lead electroencephalograph. In neither instance was an attempt made to preserve life in the fetus.

Electrodes were placed in areas corresponding to the frontal and occipital lobes. Only bipolar recordings were made. The readings were made from the right frontal to right occipital area; from the left frontal to left occipital area. Recordings were also made between the frontal areas. A similar recording was made with the occipital leads. At first the electrodes were placed into the cortex for a depth of approximately 3 mm. and readings were taken at this depth. After this cortical area ceased to record, the electrodes were inserted into a deeper position (1 cm.), and the procedure was repeated.

The fetuses were examined carefully to determine the age of each. At the present time, it suffices to state the ages without detailed embryologic explanation. The older fetus was 77 days old (CR length = 62 mm.; CH length = 95 mm.); the younger fetus was 43 to 45 days old (CR length = 16 mm.).

REPORT OF CASES

Case 1.—(77 days; intrauterine pregnancy)

In addition to the procedure previously described, silver electrodes were placed on the surface of the uterus, on the unopened amniotic sac, and on the fetal skull. These readings showed low voltage slow wave activity. This activity was constant and its rhythm was at 2 cycles per second. No fast activity was noted.

When the electrodes were inserted into the brain substance for a depth of approximately 3 mm., high voltage slow wave activity with some superimposed low voltage fast waves appeared. This activity lasted approximately 14 minutes from onset of recording (59 minutes after removal of uterus).

When the above-mentioned activity ceased, the electrodes were placed at a depth of 1 cm. and again the high voltage slow wave activity with superimposed fast activity was

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obtained. As time progressed the voltage decreased and the slow wave activity began to disappear. During this change, paroxysms of slow wave activity with fast waves superimposed appeared. All electrical activity of the brain had completely disappeared in 91 minutes from the time of ligation of the uterine arteries. Metrazol was applied topically and intracortically at this time without any revival of cortical activity. No electrocardiographic activity was noted at any time.

Case 2.—(43 to 45 days; ectopic pregnancy)

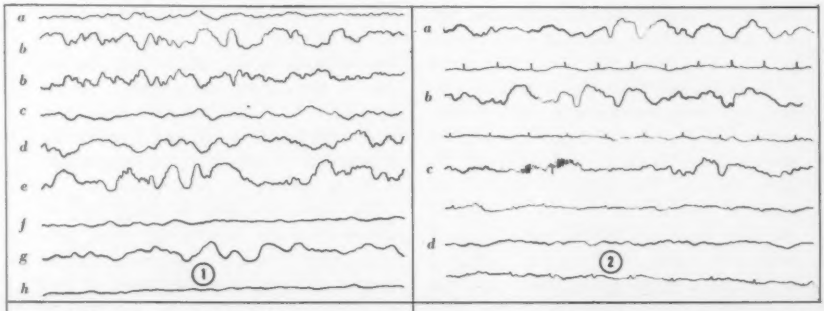
The pattern of activity in this younger fetus resembled that described above. No attempt was made to obtain readings from surface structures and the needle electrodes were placed into the substance of the brain. In this case paroxysmal rebound activity was noted from the superficial cortex. The activity from the superficial cortex completely disappeared in 62 minutes from onset of recording (72 minutes after removal of the Fallopian tube). In general, the type of waves obtained in this fetus were the same as those of the other specimen.

In addition, bursts of fast wave activity (16/sec.) from the superficial cortex and deeper structures of the brainstem were seen on two occasions. These waves resembled sleep spindles as observed in the adult electroencephalogram.

The activity from the deeper structures lasted 88 minutes. Electrocardiographic activity was noted for 78 minutes and showed progressive slowing.

DISCUSSION

The electrical activity of the fetal brain has been a matter of conjecture for years. Jasper and his associates[2] believed that the cerebral electric potentials were absent throughout most of fetal life. They found tardy prenatal development of this activity in the guinea pig. More recently Okamoto and Kirikae[3,4] studied electro-



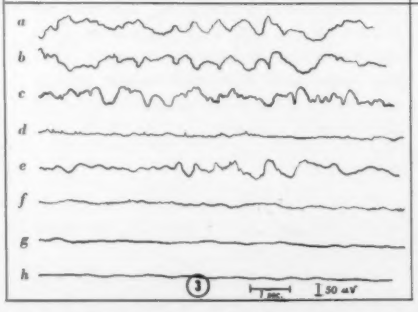


FIG. 1. A 77 day old fetus, CR length 62 mm. All bipolar readings from frontoparietal areas. (40) a. recording from surface of head. Superficially placed electrodes (depth of 3 mm.): (50) b. usual rhythm; (57) c. diminished activity. Deeply inserted electrodes (depth of 1 cm.): (70 d. usual rhythm; (74) e. usual rhythm; (80) f. diminished activity; (84) g. paroxysmal bursts of slow activity; (90) h. absence of activity. (Numbers in parentheses represent the time (in minutes) after ligation of the blood supply to the fetus.).

FIG. 2. A fetus 43 to 45 days old, CR length 16 mm. All bipolar readings from frontoparietal areas. Superficially placed electrodes (depth of 3 mm.): (30) a. usual rhythm; (35) b. paroxysmal discharge of slow activity; (42) c. sleep spindles; (65) d. diminished activity. Electrocardiogram at corresponding time is seen below each line of the electroencephalogram.

FIG. 3. Same fetus as figure 2. All bipolar readings from frontoparietal areas. Deeply inserted electrodes (depth of 1 cm.): (72) a. usual activity; (72) b. usual activity; (74) c. paroxysmal discharge of slow activity; (74) d. marked slowing of EKG with irregularity of rhythm; (80) e. diminished activity with occasional fast wave discharge; (77) f. very occasional EKG seen; (88) g. absence of activity; (78) h. absence of EKG.

encephalograms of human fetuses obtained from abdominal or vaginal termination of pregnancies. Their specimens include 16 fetuses (three to seven months), two premature infants (eight and nine months), and several full term infants. The youngest specimen they reported was three months, 8.5 cm. The recordings were chiefly monopolar. Their results showed very irregular waves of 10 to 90 microvolts with the superimposition of regular fast waves of 5 microvolts. The duration of the recordings was not mentioned, nor was the lapse of time after delivery noted. Thus the activity described may represent, for the most part, paroxysmal discharges as seen in the specimens reported here.

In the older fetus, the absence of paroxysmal activity from the superficial cortex may have been the result of delay in the placing of the electrodes into the cortex and the resultant short period of recording from this area. The types of waves noted from the superficial cortex and deep structures in both fetuses were similar and resembled the activity reported by Okamoto and Kirikae[3,4] in older fetuses. We prefer to regard this type of activity as a usual finding in the fetal brain. Although our specimens were very young, Okamoto and Kirikae[3,4] were able to demonstrate similar findings in infants born prematurely at the eighth and ninth months. The brain activity of a full term infant is quite different. Phylogenetically the same type high voltage slow waves with superimposed fast activity has been observed in mature birds,[5] in the mature frog,[6] and in the mature rabbit and mature marmot.[7]

Paroxysmal activity has not been reported previously. We believe that it may be the result of terminal electrical discharge of dying cells. The disappearance of this activity was first observed in the frontal areas. The activity disappears from the entire superficial cortex prior to disappearance of deep activity. Weinberger and his associates[8] were able to demonstrate experimentally in cats that the motor and visual cortices sustained the earliest and most profound damage following complete arrest of the circulation to the brain, while the olfactory, orbital, and temporal regions of the cortex were more resistant. This study was based on the histologic appearance of the extirpated brain. Our findings in human fetuses agree in part with their work on the brain of the cat.

Okamoto and Kirikae speculated that the origin of the brain waves which they obtained was from the brainstem, and we concur in this concept. However, fast spindles from the deep electrodes may be an indication of either early activity or even sleep in the fetus (which may represent discharge from the reticular substance). The same activity was observed in the superficial cortex and may represent transmission of activity from the midbrain by way of the reticular system to the cortex. In addition, we believe that the individual cells possess inherent electrical charge and that the disappearance of activity is a representation of dying cells in the cortical layers.

We were not able to obtain any response from the "electrically dead" fetal brain wtih Metrazol. Okamoto and Kirikae[3,4] demonstrated responses to both sedatives and stimulants; however, it may well be that this portion of their experiment was undertaken soon after the fetus was delivered, while in our case Metrazol was administered after all activity had ceased.

SUMMARY

1. Tracings were made from the brains of two fetuses, one 77 days old, the other 43 to 45 days old.

2. Bipolar readings were made and similar activity was obtained in both cases. The activity consisted of irregular slow waves with superimposed fast waves. A similar pattern (slow waves

with superimposed fast waves) of paroxysmal rebound activity was observed in both fetuses.

3. Cerebral activity disappeared initially from the frontal areas.

4. Deep activity persisted after superficial activity disappeared; this was correlated with the electrocardiogram.

REFERENCES

1. Windle, W. F.: Physiology of the Fetus, Philadelphia, W. B. Saunders Company, 1940, p. 163.
2. Jasper, H. H., Bridgman, C. S., and Carmichael, L.: An ontogenetic study of cerebral electric potentials in the guinea pig, J. Exper. Psychol. 21:63, 1937.
3. Okamoto, Y., and Kirikae, T.: Electroencephalographic studies on brain of foetus of children of premature birth and new-born, together with a note on reactions of foetus brain upon drugs, Folia Psychiat. et Neurol. Japonica 5:135, 1951.
4. Okamoto, Y., and Kirikae, T.: Electroencephalographic studies of brains of fetuses and premature children, J. Japanese Obst. & Gynec. Soc. 3:461, 1951.
5. Bremer, E. R., Dows, S., and Moruzzi, G.: Physiological analysis of the general cortex in reptiles and birds, J. Neurophysiol. 2:473, 1939.
6. Libet, B., and Gerard, R. W.: Control of the potential rhythm of the isolated frog brain, J. Neurophysiol. 2:153, 1939.
7. Motokawa, K.: Comparative studies on the brain-waves of various animals in their natural resting states, Tohoku J. Exper. Med. 50:297, 1949.
8. Weinberger, L. M., Gibbon, M. H., and Gibbon, J. H.: Temporary arrest of the circulation to the central nervous system, Arch. Neurol. & Psychiat. 43:961, 1940.

■ *What is the cause of pain produced by the irritation of the anterior roots of nerves?* According to Carus, the nervous loops, which he thought existed in the muscles, give an easy explanation of the facts discovered by Magendie. Unfortunately for this explanation the existence of nervous loops in muscles is now disproved. Indeed, even in the skin there is good ground to doubt the presence of many loops. Some experiments, which we have made, render it probable that the pain caused by the irritation of the anterior roots is exactly of the same nature as that of cramps, and that both the pain of cramps and the pain which we will call recurrent, to avoid circumlocutions, depend upon a peculiar kind of irritation of the sensitive nerves of muscles. The theory we will propose is also applicable to many pathological and physiological phenomena, which have puzzled for a long while both practitioners and physiologists, and which seem, indeed to be very plain and natural now that we have the key to their explanation.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Acute Hemiplegia In Infectious Mononucleosis

Isadore Green, M.D.

NEUROLOGIC COMPLICATIONS of infectious mononucleosis are not rare. Cases previously diagnosed as infectious polyneuritis (Guillain-Barré syndrome), lymphocytic choriomeningitis, and certain meningoencephalitides in isolated and combined form and serous meningitis were found to be associated with infectious mononucleosis.

Silversides and Richardson[1] reviewed 59 cases, in eight of which death resulted from neurologic complications. Autopsy showed engorgement of the veins and capillaries of the meninges, with infiltration by mononuclear cells into the anterior nerve roots at all levels. Perivascular hemorrhages, mild ganglion cell disease, mild to moderate infiltrations by inflammatory cells in the meninges, and neuraxis and invasion of the posterior roots and spinal ganglia have also been reported.[2–8]

According to an observation by Griffith,[9] neurologic complications of many infectious diseases, more particularly the exanthems, appear to be increasing and tend to follow a poliomyelitis epidemic. Since 1950, the so-called peak year of polio, this seems to have occurred. In emphasizing the role of infectious diseases in the production of neurologic complications, Griffith described the following syndromes: 1) symptoms of diffuse cerebral involvement (meningism); 2) multiple focal or diffuse lesions of the nervous system; 3) single focal cerebral lesions; 4) cerebellar syndromes; 5) spinal syndromes; 6) optic neuritis; 7) mental and personality changes.

These studies and the reports of neurologic complications in infectious mononucleosis appearing since 1950 certainly suggest that the syndrome may be anticipated to appear in infectious mononuclosis. Diffuse cerebral involvement, multiple focal and diffuse lesions of the nervous system have already been described and attest to the neurotropic character of the virus of this disease.

The following case presents evidence of an isolated focal lesion, at least with regard to the clinical manifestations.

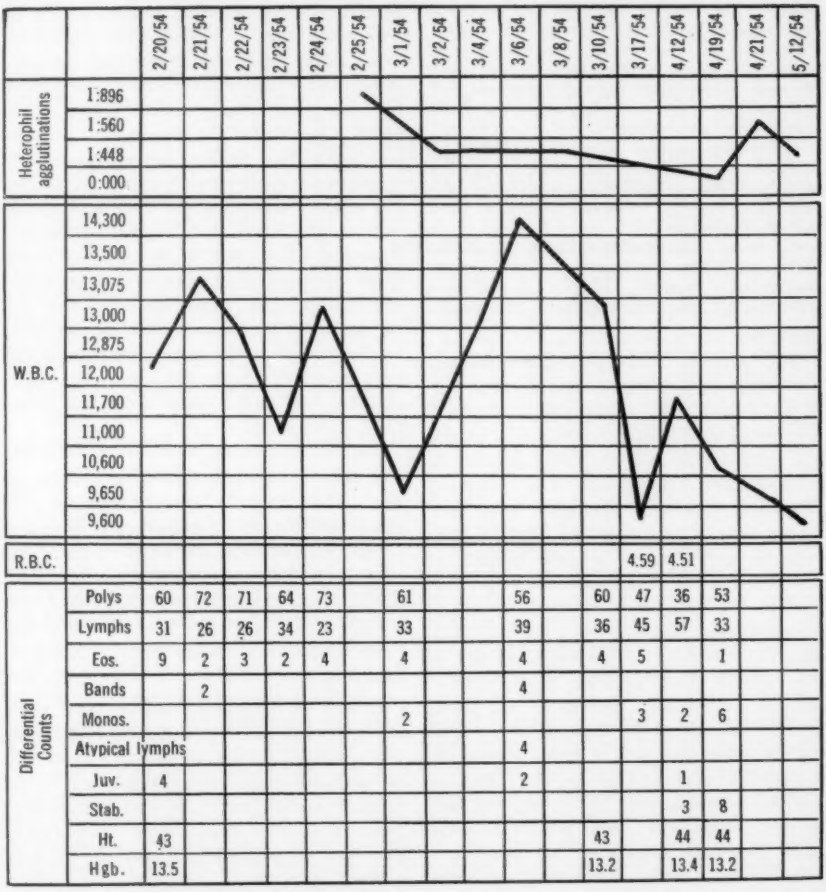
PRESENTATION OF CASE

A 17 year old white Jewish girl was admitted in semicomatose condition to the Winthrop Community Hospital, on February 20, 1954, with a history of sudden collapse while in conversation with some friends on the street.

For several days prior to the onset of hemiplegia, the patient had complained of malaise, sore throat, headache, and some subjective vertigo; other than this the history was essentially negative and noncontributory.

Examination: The head was free of laceration. Pupils were equal and regular, and reacted well to light and accommodation. There were no enlarged glands or stiffness in the neck. Heart sounds were within normal limits, with no murmurs, and regular rhythm and rate. Lungs were clear and resonant throughout, with no rales or dullness. Abdomen was soft and no masses were palpable. There was right-sided hemiplegia, with a hypertonic right arm, flaccid right lower extremity, right ankle clonus, right Babinski sign, and abdominal reflexes absent on right.

From the neurologic clinic of the Jewish Memorial Hospital, and the department of neurology, Tufts College Medical School, Boston.



		2/20/54	2/21/54	2/22/54	2/23/54	2/24/54	2/25/54	3/1/54	3/2/54	3/4/54	3/6/54	3/8/54	3/10/54	3/17/54	4/12/54	4/19/54	4/21/54	5/12/54
Heterophil agglutinations	1:896																	
	1:560																	
	1:448																	
	0:000																	
W.B.C.	14,300																	
	13,500																	
	13,075																	
	13,000																	
	12,875																	
	12,000																	
	11,700																	
	11,000																	
	10,600																	
	9,650																	
	9,600																	
R.B.C.														4.59	4.51			
Differential Counts	Polys	60	72	71	64	73		61			56		60	47	36	53		
	Lymphs	31	26	26	34	23		33			39		36	45	57	33		
	Eos.	9	2	3	2	4		4			4		4	5		1		
	Bands		2								4							
	Monos.							2						3	2	6		
	Atypical lymphs										4							
	Juv.	4									2				1			
	Stab.														3	8		
	Ht.	43											43		44	44		
	Hgb.	13.5											13.2		13.4	13.2		

FIG. 1. Serial blood counts and heterophil values.

Neurologic examination showed total right-sided hemiplegia; hyperactive deep responses more marked on right; right Babinski; left plantar response diminished; total right-sided hemihypesthesia; no visual or field defect; no nystagmus; fundi normal; bilateral Hoffman signs; aphasia with marked motor components; slight difficulty in comprehension; and spinal fluid clear, dynamics normal, initial pressure 185, final pressure 85.

Chest films on admission showed very slight hilar enlargement and slight moderate peribronchial thickening around the hila and in the bases, neither condition very marked. The lungs were negative, with nothing to suggest tuberculosis, consolidation, pleural effusion, abscess, collapse, or other pathology. Heart was normal in size, shape, and position, with a cardiothoracic ratio of 13.0 over 28.0. It seemed unlikely that there was anything in the heart or lungs to account for the patient's condition.

Skull films showed that the bones of the skull were normal in position, outline, and density. The vascular markings were normal, and there was no evidence of erosion, unusual calcification, or sclerosis. The pineal was not seen. There was no evidence of congenital abnormalities, tumor, trauma, or inflammatory

change. The base of the skull was normal in appearance. The mastoids were well developed. There was no evidence of infection or other pathologic change in that region. What could be seen of the upper cervical spine was normal and the bony structures about the facial region were not unusual.

Laboratory findings: Cerebrospinal fluid examination on February 20, 1954, showed a slightly yellow colored fluid, with total protein 42.0 mg. per 100 cc., chlorides 135.0 milli-equivalents per liter, and a flat gold curve. Serial blood counts and heterophile values are shown in figure 1. Agglutinins for typhoid, paratyphoid, brucella, blood cultures, and other routine laboratory tests were all normal.

DISCUSSION

The question which this case proposed is whether or not the sudden development of hemiplegia can be considered a neurologic complication of infectious mononucleosis with invasion of the cerebrum or an isolated unrelated episode. The symptoms of malaise, headache, dizziness, fever, sore throat, coryza preceding the cerebral episode by several days, and the findings of positive heterophil agglutinations tests in a relatively high titer, in the absence of serum sickness, warrants the conclusion that infectious mononucleosis actually existed in this patient. Since invasion of the central nervous system does apparently take place in this disease and the number of reported cases confirms this fact, it seems reasonable to postulate at least, that the hemiplegia is a related phenomenon. In this instance had no heterophil test been performed one might have well concluded that this represents an acute episode of multiple sclerosis similar to other reported instances. Up to this point, careful studies have shown no other cause for the syndrome and the progress of the patient has been characterized by slow and steady improvement. One might suggest that the persistence of negative spinal fluid findings argues against the invasion of the central nervous system by the virus. Negative spinal fluid findings are not unusual in virus infections of the encephalon. The cases of the Guillain-Barré type of complication presented definite abnormalities in the spinal fluid, but this can be explained by the proximity of the roots to the subarachnoid space, whereas in the case described above the lesion was intracerebral and more remote from the spinal fluid reservoir.

Further studies are necessary to establish a definite relationship, and the findings in this and other cases reported indicate that the possibility of infectious mononucleosis should be considered in the presence of an acute neurologic syndrome in children and young adults. Heterophil tests may bring to light many more instances of neurologic complications.

CONCLUSION

A case of infectious mononucleosis with acute hemiplegia is described. Heterophil and absorption tests should be performed in cases which present a syndrome of infectious disease with neurologic complications. Where no other known cause exists, infectious mononucleosis should be suspected.

Grateful acknowledgment is made to Dr. J. Gregorie for his help and counsel during the patient's stay at the Winthrop Community Hospital, and to the late Dr. Leon Levinson of the medical service of the Jewish Memorial Hospital for his assistance in this case.

REFERENCES

1. Silversides, J. L., and Richardson, J. C.: Neurologic complications of infectious mononucleosis, Canad. M. A. J. 63:138, 1950.
2. Allen, Fred H. Jr., and Kellner, Aaron: Cerebral lesions, Am. J. Path. 23:463, 1947.
3. Peters, Clifford H. et al: Neurologic manifestations of infectious mononucleosis with special reference to the Guillain-Barré syndrome, Arch. Int. Med. 80:366, 1947.
4. Hoyne, R. M.: Involvement of central nervous system in infectious mononucleosis. Report of case with ataxia and nystagmus, Arch. Neurol. & Psychiat. 63:606, 1950.
5. Creaturo, N. E.: Infectious mononucleosis and polyneuritis. Report of case with facial diplegia treated with 2, 3,-dimercaptopropanol, J.A.M.A. 143:234, 1950.
6. Bercel, N. A.: Infectious mononucleosis, encephalitis, epilepsy, Am. J. M. Sc. 224:667, 1952.
7. Freedman, M. J., Odland, T., and Cleves, E. A.: Infectious mononucleosis with diffuse involvement of the nervous system. Report of a case, Arch. Neurol. & Psychiat. 69:49, 1953.
8. Garvin, John S.: Infectious mononucleosis with Guillain-Barré syndrome, J.A.M.A. 151:293, 1953.
9. Griffith, G.: Neurological complications of some infectious diseases, Edinburgh M. J. 59:492, 1952.

Neurology

BOOK REVIEWS

Aphasia Therapeutics

Mary C. Longerich, Ph.D., and Jean Bordeaux, Ph.D. 1954. New York: The Macmillan Co. 185 pages, $3.75.

THIS MANUAL for the rehabilitation of the aphasic patient is, for the therapist, a well designed introduction to the vast problem of aphasia. Early chapters sketch briefly the history of our ideas about aphasia, citing especially the contributions of Gall, Broca, Trousseau (who applied the term "aphasia" to these disturbances), Hughlings Jackson, Head, Henschen, Goldstein, and Nielsen. Chapters on terminology and symptomatology mirror the complexity and confusion which still becloud the subject.

A most valuable chapter concerns the appraisal of the patient's capacities — a necessary prelude to discriminating therapy. It is pointed out that success requires that clear goals be set before the patient, and that both therapist and patient envisage a cheerful prognosis. It is well to begin with the problem of greatest concern to the patient. The interesting observation is made that, other things being equal, receptive aphasia is less hopeful than the expressive variety. Other important facts are stressed: that the therapy of aphasia demands close rapport and cooperation between therapist and patient; that calm and persistent drilling, with simultaneous use of several sensory modalities, must be combined with imaginative stimulation of interest and careful apportionment of tasks to ability; and that such therapy requires skillful individualization. The practical business of teaching is meticulously set forth in a long chapter dealing with the many varieties of aphasia and the specific technics best adapted to each. Reasonable suggestions are made in wholesome detail.

A final chapter on the psychologic aspects of the therapy of aphasia rightfully stresses that the nuances of personality require adaptability of approach and method. In general, therapy must be directed to the support of the patient's ego and the bestowal of ego satisfaction. The interesting point is made that the receptive aphasic is more seriously disturbed by injury to his self-esteem and more subject to catastrophic discouragement than is the expressive aphasic. This observation is surprising in view of the lack of insight of the receptive aphasic. The authors wisely emphasize the necessity for an apraisal of the premorbid personality of the patient and an adaptation of method and technic to the total individual in his nonlinguistic as well as linguistic needs. The philosophy of the book is well summarized in the final paragraph: "In brief, the psychological goal in the . . . . treatment of an aphasic victim should be to aid him in recovering his integrity as a well-functioning individual."

As stated above, this book is a practical manual for the guidance of the therapist who is not a neurologist. It would be cap-

tious and stuffy to complain that the conception of aphasia set forth in a book of this sort is rigid and sketchy. The authors' approach is eclectic, and their classification of aphasia, synthesized from a tremendous and diverse literature, is marked by minute subdivisions and overlapping categories, sometimes of doubtful validity. In no field so often as in aphasia do we find distinctions without a difference and areas without boundaries. These authors are not to blame; they have followed in others' footsteps whose vast books wade through aphasia with no greater clarity. Errors are unavoidable; though perhaps debatable, some appear here. For example, it seems to reverse logic to consider agnosia as a type of receptive aphasia, or apraxia as a form of expressive aphasia. Surely agnosia and apraxia involve nonlinguistic as well as linguistic functions, and are larger categories of which aphasia is merely one aspect. Occasional loose expressions lead to confusion, such as that aphasia often shows up in neurotic patients, or that the expressive aphasic's inability to speak the word "apple" arises from his "inability to think of the idea of apple long enough."

This book is thus not a notable exposition of aphasia in its theoretical or descriptive aspects. Its defects in this regard are, however, those which mar much more ambitious treatises. Upon viewing the whole subject of aphasia, agnosia, and apraxia, one must confess great discontent. Our concepts are far too static, anatomic, and mechanical. We have not yet freed ourselves from the phrenologic bias inherited from the doctrine of self-contained "centers"—a doctrine which is dying a hard death. One may anticipate a much simpler formulation of the perplexing phenomena of aphasia when a more dynamic theory of neural function shall have been devised.

Such criticisms in no wise impair the appraisal of this book as a valuable manual of practical technics in treating aphasic persons. Its specific suggestions, expressed in clear and concise language, make it a great help to the therapist. The bibliography offers the interested student a useful guide to further reading.

R. P. M.

The Epilepsies: Electro-Correlations.

Henri Gastaut, M.D. 1954. Springfield, Ill.: Charles C Thomas, Publisher. 149 pages, $4.75.

THIS MONOGRAPH summarizes the experimental observations as well as the theoretical implications of ten years' work by Gastaut in the field of epilepsy. One of the most important features of the work is the fact that it is based upon clinical and electroencephalographic observations of actual seizures provoked by a variety of activation techniques, chiefly photic stimulation and Metrazol injection.

The author's interpretations of his findings are provocative and will undoubtedly have a lasting effect upon both experimental and clinical phases of epilepsy. There is much in Dr. Gastaut's exposition that invites discussion but very little that does not add to our too meager knowledge of the activity of the central nervous system.

In addition to the originality of much of this monograph the presentation of many aspects of our existing knowledge of the epilepsies makes a very worthwhile summary. There is an excellent review of the current hypotheses regarding the importance of subcortical elements in both partial and generalized epilepsies. Gastaut's work adds considerable weight to the importance of the concept of a centrencephalic mechansim in many clinical forms of epilepsy and offers a physiologic framework in which a number of apparent clinical inconsistencies can be resolved.

The review of the etiologic, clinical, and therapeutic classifications is useful. The outline of general principles of medical

therapy and the suggested criteria for selection of cases for surgical treatment is thoughtful and will be helpful to the clinician. The electroencephalographic observations are important. No detailed analysis or discussion of the subject is attempted, however. One can easily gather from the book the growing contribution of electroencephalography to epileptology.

Thus this monograph is of value to both research worker and clinician. The absence of references is the only major criticism of this publication.

A. L. D.

A Dynamic Psychopathology of Childhood

Lauretta Bender, M.D. 1954. Springfield, Ill.: Charles C Thomas, Publisher. 296 pages, $7.50.

This is the third in a series of Bellevue studies on child psychiatry. The first book of the series, *Child Psychiatric Techniques*, described the diagnostic and therapeutic methods employed in the studies of children comprising the background of this third volume, as well as the second, *Aggression, Hostility and Anxiety in Children*. This is not in any sense a textbook of psychopathology in childhood, but rather a collection of papers, some of which have been published previously in journals in whole or in part. While the book is Bender's throughout as expressed through her editing and formulations, it is admittedly an extension or elaboration of Schilder's ideology. Bender's Schilder is more intelligible than is Schilder himself. A number of her associates have collaborated with Dr. Bender in these studies, to whom she has given acknowledgment in the preface and the footnotes to each chapter.

Ten topics of special interest are covered, some of which are very significant to the understanding of every day psychology of children. The chapters on hallucinations and on imaginary companions are concerned with the phantasy life of children. While many consider hallucinations and excessive fantasy presumptive evidence of psychosis, from the case studies of 17 children having hallucinatory experiences who did not develop psychosis, it is concluded they occur as a result of a discrepancy between the child's needs and drives and the reality offered him. They occur on a background of unsatisfactory relationships between the child and parent. In the chapter on imaginary companions it is concluded that such fantasy is a good prognostic sign of "ego strength" regardless of the personality problem which the child may otherwise present.

In the chapter on impulsions, compulsions, and obsessions, impulsions are defined and related to specific behavior disorder, often associated with compulsions and obsessions. The seriousness of these manifestations and their occurrence in organic disease, as well as their relation to schizophrenia, is discussed. Their resistance to therapy has its adult counterpart.

Those concerned with the current social problems of sexual psychopathology which adorn the newspapers will find the chapter on sexual expression and identification conflicts has some implications on the origin of these distressing disorders in adults as well as understanding of the several types of sexual activity among children. On the whole those problems involving sexual experience of children with adults have more serious portent than the sex play between pre-adolescents.

Another chapter of special interest is that on children's reaction to death in the family, in which it is concluded that children react to this event with all the psychologic

mechanisms that are known in deep grief and mourning in the adult, experienced as depression, anxiety, and guilt.

The chapter on comic books and the ideology of children should be welcomed by all who counsel with parents and educators. After careful consideration of all aspects and many kinds of comics, it is advised that with some screening, the comic is acceptible literature as a means of dealing with cultural and social problems on the level of childhood understanding.

Other chapters are concerned with language and symbol development and with children's concepts of the insides of their bodies and fantasies of introjected objects.

This book will be of great interest to all who are engaged in the practice of child psychiatry. Those who are engaged in the practice of adult psychiatry will find the origins of much that characterizes adult neurotic and psychotic behavior. The text is richly illustrated by case material.

M. G. M.

Nature and Nurture

John L. Fuller. 1954. Garden City, N. Y.: Doubleday and Company. 38 pages, 85 cents.

In this 38 page brochure, the manifest purpose has been to assay the role of heredity in the determination of behavior in light of the more recent knowledge gained from the laboratory and research worker.

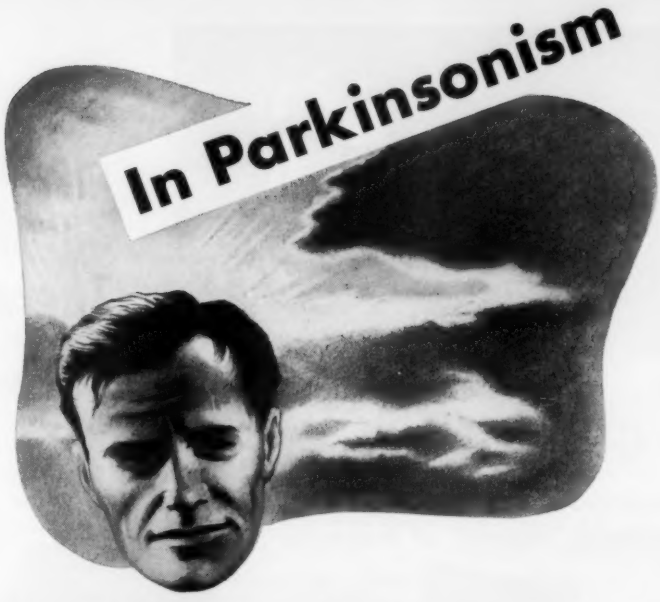
The author, a biologist, reviews the contributions in the field of mental disease and behavioral disorder from the genetic approach. He points out the relative simplicity of predictions from the application of genetic principles in determining disorders due to dominant genes, using the well documented Huntingtons' chorea as an example. Here, however, the reviewer was let down, for Fuller states that some carriers of the gene do manage to live out a normal life span without showing its effects, but they can still transmit the disease to their children and afflict a new generation. This is contrary to the belief held by clinical neurologists and by the Huntingtons. It is generally taught that the offspring of those who fail to develop the disease would themselves neither develop the disease nor transmit it.

As implied by Fuller, the real dilemma in assessing the role of heredity derives from genetic factors that are elusive – the recessive genes, and even more elusive – the polygenes. There is no methodology for predicting their influence. Herein lies the riddle of genetic determination of physiologic and psychologic traits. It is the author's belief, from the application of experimental data to human genetics, that schizophrenia and manic depressive psychoses are due to multifactoral inheritance rather than to recessive or dominant factors, and further that the degree of resistance or susceptibility is part of the multifactoral inheritance.

The author believes, as is stated in the introduction, that "heredity is the capacity to utilize the environment in a particular way. There is then no nature-nurture dichotomy." Each human being is the result of the interaction between his genes and his culture.

This monograph provides an easily assimilated review of this ancient problem. The author's conclusions are those held by most students of behavior today.

M. G. M.



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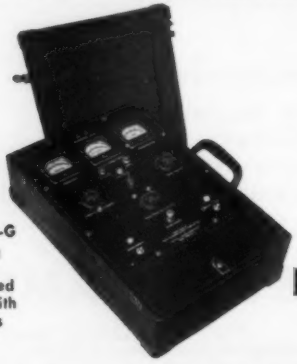

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AMERICAN ACADEMY OF NEUROLOGY

EEG Society To Meet in Chicago The ninth annual meeting of the American Electroencephalographic Society will take place at the Palmer House, Chicago, on June 10-12, immediately preceding the annual meeting of the American Neurological Association. The scientific sessions will include two symposia: one on microelectrodes under the chairmanship of Herbert H. Jasper; the other on clinical EEG interpretation of head injuries under the chairmanship of Frederic A. Gibbs. The annual banquet is scheduled for Saturday, June 11.... Communications should be sent to Dr. W. T. Liberson, Secretary. American EEG Society, VA Hospital, Northampton, Mass.

Greenfield to be President Of International Congress Dr. J. G. Greenfield, distinguished English neuropathologist and honorary consultant to the National Hospital, Queen Square, London, now in the U. S. A. as a visiting scientist to the National Institute of Neurological Diseases and Blindness, will be inducted as president of the Second International Congress of Neuropathology, to be held in London (Sept. 12-17).... The executive committee of this congress, under the chairmanship of Prof. Dorothy Russell, already has formulated a tentative timetable and program, which proposes round table discussions of tissue culture; the teaching of neuropathology and the training of neuropathologists; the planning of laboratory research in mental disease; and the importance of genetics in the study of insanity and mental deficiency. Lady Brain, chairman of the ladies' committee, will organize examinations and other social events. The famous London Guildhall has been reserved for the official banquet.... Dr. W. H. McMenemey, of Maida Vale Hospital for Nervous Diseases, is secretary-general of the congress. Chairman of the American committee is Dr. Armando Ferraro, 722 West 168th Street, New York 32, N. Y.

Neuroradiologists To Meet in London The Fourth Symposium Neuroradiologicum will be held in London (Sept. 13-17). Particularly welcome are radiologists, neurologists, and neurosurgeons. The scientific sessions will take place at the University of London, Malet Street, W. C. 1.

Subjects for discussion include cerebrovascular disease; localization of intracranial tumors by isotopes; applications of stereotaxometry; and selected papers on a variety of neuroradiologic subjects. Also tentatively arranged is a joint half-day session with the Second International Congress of Neuropathology to discuss the problem of tentorial herniation of the uncus.... Application forms and further information may be obtained from Dr. R. D. Hoare, Secretary, Symposium Neuroradiologicum, The National Hospital for Nervous Diseases, Queen Square, London, W. C. 1.

* * * * * *

NINDB Plans Collaborative Project in Cerebral Palsy The National Institute of Neurological Diseases and Blindness has initiated a multidisciplinary, collaborative research project in cerebral palsy. Purpose of the project is to integrate more sharply the clinicopathologic forms of these conditions, create new etiologic research leads, and implement current experimental investigations. The organization of the project is geared to collect and correlate the results of studies in cerebral palsy now being pursued independently in many disciplines: clinical and experimental neurology, pathology, psychology, pediatrics, obstetrics, and orthopedic surgery. To achieve these ends NINDB will serve as a coordinating center or central laboratory for special evaluations and correlations of clinical histories and postmortem specimens received from several collaborating hospitals and institutions throughout the country. The collaborating institutions, whether they are NINDB grantees or local contributing hospitals, will be completely free to do as much of their own analyses as desired and to publish their reports independently. In turn, the analyses and correlations prepared by NINDB will be submitted to all the collaborating institutions and a statistical report of the total study will be distributed.... In order to provide uniform clinical and pathologic criteria for the project, an ad hoc committee of 15 scientists, under the chairmanship of H. Houston Merritt, has convened and is preparing a special protocol for the collection of clinical and postmortem data. On this committee are representatives from the various clinical and basic disciplines pursuing research in cerebral palsy.

Multiple Sclerosis Society Presents Research Fellowship Program The National Multiple Sclerosis Society has announced a limited number of research fellowships for students and scholars who wish to enter the field of research related to multiple sclerosis and demyelinating diseases. The society offers three types of awards: postdoctoral research fel-

lowships to qualified candidates holding a doctorate in medicine or related fields, with a basic annual stipend of $4,000 to $5,000, varying with previous training and family dependency status; scholarship awards will be made to qualified candidates holding a doctorate in medicine or related fields and showing competency in biologic investigations. This award carries an annual stipend of $6,000 to $8,000 based on record and experience.... These awards are made for one calendar year, though one or two additional years of fellowship support may be requested. Application may be made at any time and awards will be announced twice yearly -- in June and in December. The awards are not intended to support the routine clinical training of a resident whose primary aim is specialty board certification.... Grants up to $500 may be made to the sponsoring institution, upon application, as reimbursement for costs incurred by the Institution incident to the training program, and an annual travel allowance of $150 will be allowed. All applications and communications should be forwarded to Dr. Harold R. Wainerdi, Medical Director, National Multiple Sclerosis Society, 270 Park Avenue, New York 17, N. Y.

New Diplomates In Neurology At the examination of the American Board of Psychiatry and Neurology, held in New Orleans, La. (February 28-March 1), 13 candidates were certified in neurology. The successful candidates are: George A. Berglund, Madison, Wisc.; Lenora Virginia Brown, Pittsburgh, Pa.; Edward A. Cary, VA Hospital, Ann Arbor; John R. Finkle, Berwyn, Ill.; Guy M. Hunt, Loma Linda, Cal.; Donald A. Johnson, Memphis, Tenn.; Gene Martin Lasater, Minneapolis; Claude M. Lowry, Ann Arbor; Simon Maringer, New York, N. Y.; Henry Augustus Peters, Madison, Wisc., psychiatry and neurology; Seymour Solomon, USAF Hosp., Maxwell AFB, Ala.; Robert Allen Utterback, Iowa City; and Laurence M. Weinberger, Akron, Ohio.

* * * * * *

Harold Stevens Heads Neurology At George Washington University Harold Stevens, formerly associate professor of neurology at the Georgetown University School of Medicine, has been appointed professor and head of the neurology department at George Washington University to succeed Dr. Walter Freeman, who has moved to California. The new appointment was effective March 1, 1955.

Cerebral Palsy Group To Meet in Memphis The American Academy for Cerebral Palsy (Dr. Lenox D. Baker, president) will hold its annual meeting in Memphis, Tenn. (October 10-12). The meetings are open to members of the medical

and allied professions interested in cerebral palsy. The three-day program will include instructional courses in various phases of cerebral palsy, as well as scientific sessions. Invitations to attend may be obtained, upon request, from Dr. Robert A. Knight, Secretary-Treasurer, 869 Madison Avenue, Memphis 3, Tenn. Requests for hotel reservations are to be sent directly to Mr. Scott Stewart, Manager, Claridge Hotel, convention headquarters, Memphis, Tenn.

Here and There Dr. Macdonald Critchley will fly to the U. S. early in May to participate in the centennial celebration at St. Elizabeths Hospital, Washington, D. C..... Dr. Robert Wartenberg, having reached the age of 67 on the first of July 1954, was retired as professor of clinical neurology at the University of California, but recently has been recalled to active duty on the teaching staff of this medical school, an event which has never happened before in its history.... The program executive committee for the Sixth International Neurological Congress will meet in Brussels (Sept. 7-8) to formulate plans for the Sixth International Neurological Congress, to be held in 1957.... Seymour S. Kety is the new chairman of the Research Advisory Board of the United Cerebral Palsy Association, succeeding Sidney Farber.... Gene M. Lasater, instructor in the division of neurology, University of Minnesota Medical School, has accepted an appointment as assistant professor in the department of neurology and psychiatry at the University of Tennessee College of Medicine, Memphis....

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AWARD GIVEN "MARCH OF MEDICINE" FOR OUTSTANDING PROGRAM ON MENTAL ILLNESS

For "their outstanding contribution to public understanding of the problem of mental illness" the American Medical Association and Smith, Kline & French Laboratories, Philadelphia, have been honored by the National Association for Mental Health.

The tribute to "The March of Medicine" telecast entitled "Search for Sanity" was presented by Mrs. Felix duPont, board member of the mental health group, to Dr. Leo H. Bartemeier, chairman of the A.M.A. Committee on Mental Health, and Mr. Francis Boyer, president of Smith, Kline & French Laboratories.

The telecast, presented by the A.M.A. and S.K.F. over the National Broadcasting Company's television network, took the American public on an unprecedented tour of one of the country's largest mental hospitals, Hudson River State Hospital in Poughkeepsie, N. Y. It reported on the care and treatment of patients and on research underway in this field.

OUTLOOK FOR ABBOTT IN 1955 IS GOOD

President Ernest H. Volwiler of Abbott Laboratories, North Chicago, Illinois, says: "The scientific work of the past year or more has led to several new drugs and pharmaceutical preparations, some of which are already on the market; others being clinically tested. We expect some to reach the marketing stage this year."

ATABRINE FOUND EFFECTIVE AGAINST PETIT MAL ATTACKS

The antimalarial drug Atabrine, made by Winthrop-Stearns, Inc., New York City, effectively combats petit mal seizures, either alone or in combination with convulsions. It is administered in 0.1 gm. tablets, in dosages ranging from 0.1 to 0.4 gm. a day. There is considerable agreement among clinicians today on the principles of treatment for epilepsy. Most concede that the drug to be used and the dosage must be individualized due to each patient's variation in tolerance and need for medication. Effects of full doses of the least toxic drug should be tested first and the drug withdrawn if therapy proves unsuccessful. When one drug used singly fails, seizure control is often achieved by a combination of drugs in full dosage. There is need for caution against sudden withdrawal of effective medication which may act as a trigger to a series of seizures.

WARNER-LAMBERT MERGER

Stockholders of Warner-Hudnut, Inc. and The Lambert Company have approved the merger of their companies. The new company will be known as Warner-Lambert Pharmaceutical Company. It will have annual sales of nearly $100,000,000 and about 7,000 employees engaged in world-wide operations.

Ranking high among the diversified drug companies in the United States, Warner-Lambert's major divisions are engaged in manufacturing and distributing ethical pharmaceuticals, proprietary drugs, toiletries, brushes and combs, and custom-molded plastics. The company's foreign operations include branches and affiliates in 18 countries; sales outlets in 100.

E. Roth Janes, operations vice-president of Warner-Chilcott Laboratories, Morris Plains, New Jersey, has been appointed chairman for the 1955 campaign of the Morris County Chapter of The American Cancer Society.

SHERMAN LABORATORIES EXPANSION

The steady growth of the ethical pharmaceutical industry is again demonstrated by the physical expansion of Sherman Laboratories, Detroit, Michigan. This organization will move to a new building this summer, which triples the former operations space. According to an executive of the organization, part of the need for this expansion is the increasing demand for Protamide — a product introduced a few years ago for the therapeutic relief of nerve root pain — which has filled a definite need in practical therapeutics.

Sherman Laboratories, founded in 1907 by G. H. Sherman, M.D., has been in its former and original location for over forty years and was one of the pioneers of vaccines and vaccine therapy in the United States. The laboratory expanded into general pharmaceutical manufacture and today is especially noted for its parenteral products and original prescription specialties. Information to the profession on products manufactured is supplied by a national force of professional representatives, medical journals and direct mail.

The company extends a cordial invitation to visit the new laboratory when in Detroit.

LEDERLE MEDICAL SCHOOL FACULTY AWARDS

Fourteen outstanding medical school teachers and researchers have been named to receive grants totalling $270,500 this year from the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, New York.

The awards, believed to be the first of their kind in this field, are intended to augment salaries or to help schools fill teaching or research positions. Their basic purpose is to help assure that more promising medical men can afford to remain in teaching and research work at schools and universities. One of the recipients is Dr. Eugene Donald Grim, instructor in the Department of Physiology, University of Minnesota Medical School. (3 years $22,000). Another is Dr. Frances O. Kelsey,

Associate Professor of Medicine at the University of South Dakota. (3 years $22,500).

All grants made through the Lederle Medical Faculty Awards Committee are for a term not exceeding three years, and no single grant can exceed $10,000 per year.

LAKESIDE REPORTS ON NEW DRUGS

Neurologists concerned with the peace of mind of patients with peptic ulcer will be especially interested in the cholinolytic Piptal, for the relief of ulcer painspasm, day or night, without threat of urinary retention or constipation. The new medicament is closely related to Dactil, is distinct from any available anticholinergic and accomplishes its results by normalizing gastric motility and secretion through postganglionic parasympathetic inhibition. Piptal is not yet to be had for prescription but a clinical supply will be mailed if request is made to the scientific director of Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin, Dr. H. L. Daiell.

Reaching its thirtieth anniversary, Lakeside Laboratories reports also on a search for an unusual drug that can protect the neurologist's asthmatic patient against attacks even when taken orally. The chief of the company's medicinal chemistry division reveals that the idea motivating the studies has been to incorporate pressor amines into the arterenol molecule. Approximately sixty such brochodilators have been synthesized and tested in animal studies, against histamine or mecholyl-induced asthma.

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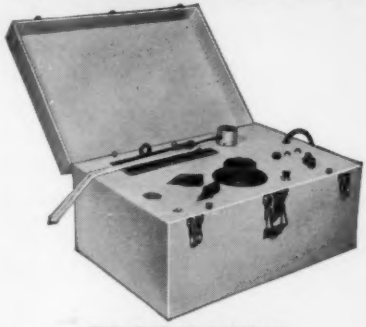

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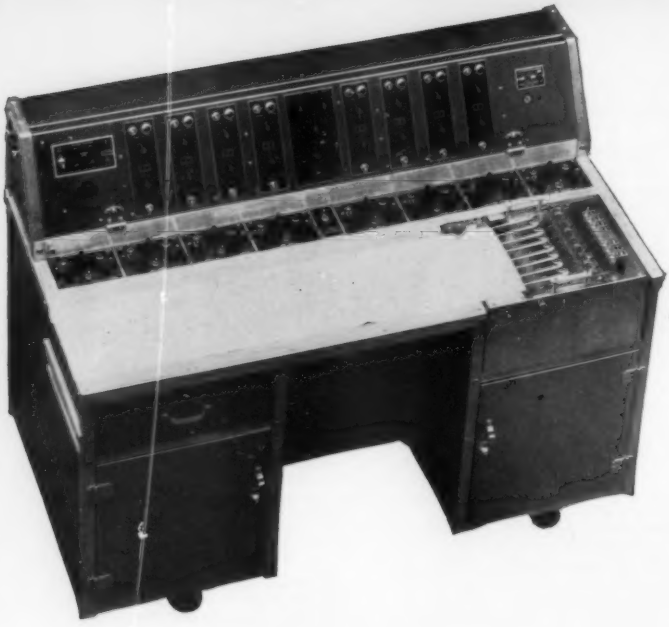

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*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.

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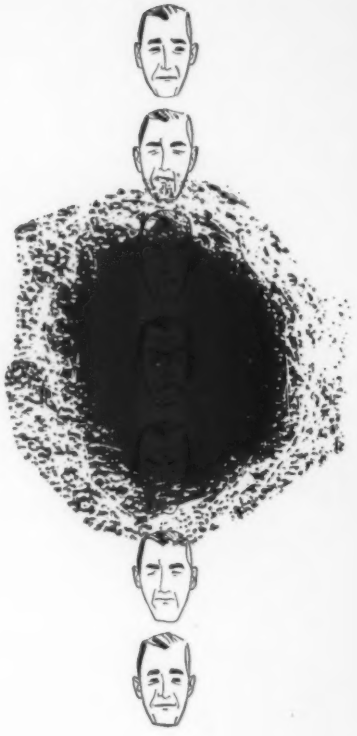

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1. Meller, R. L., and Resch, J. A.: *Postgrad. Med.*, 6:452, Dec., 1949.
2. Reder, E. L.: *New York Jour. Med.*, 54:1659, June 1, 1954.
3. Berris, Harold: *Neurology*, 4:116, Feb., 1954.
4. Carter, Sidney; and Merritt, H. H.: *Am. Pract. & Digest Treat.*, 3-547, July, 1952.

Mebaral, trademark reg. U.S. Pat. Off., brand of mephobarbital

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